THE
BRITISH JOURNAL OF SURGERY

VOL. XLIII MARCH, 1956 NO. 181

CRITICAL REVIEW

THE RECONSTRUCTION OF ARTERIES

BY C. G. ROB, H. H. G. EASTCOTT, AND K. OWEN
ST. MARY'S HOSPITAL, LONDON

THE development of this branch of surgery during the last ten years has been so rapid that artery banking, which was practised clinically for the first time by Gross, Bill, and Peirce (1949), is now nearly out of date. In fact, we prefer a plastic prosthesis for arteries of the size of the human external iliac or larger, and consider that the results are as good with less risk to the patient and considerably less trouble for the surgeon and his team.

METHODS OF VASCULAR RECONSTRUCTION

The best method of restoring the continuity of a blood-vessel is by a *direct suture* either of a lateral defect or by an end-to-end anastomosis. It is difficult to discover who was the first to suture a lateral defect in a blood-vessel. Höpfner in 1903 published a review of the literature, and he stated that Lambert of Newcastle was the first surgeon to write about vascular suture and that Hallowell in 1759 was the first to perform it on a patient. He sutured a lateral defect in a brachial artery, the limb survived but it is not certain whether the vessel remained patent or not. The first end-to-end anastomoses were probably performed by Murphy (1897). The modern technique of vascular anastomosis using two or three stay sutures and then a continuous everting mattress or over-and-over suture of fine silk was worked out by Carrel (1907) and has not altered since. In our view, a direct anastomosis should be employed whenever it is anatomically possible; it is the ideal method of repairing an injury, and it is surprising how often it is possible to close the gap by direct suture after a diseased segment of an artery or vein has been resected. This is particularly so in patients with arteriosclerosis. An arteriosclerotic artery is often lengthened and tortuous; this after mobilization allows the surgeon to close a fairly long defect by direct suture. During the past five years we have repaired the arteries of six elderly patients in this way. A typical example was a man aged 74: during the course of an operation for carcinoma of the mouth a mass of lymph-nodes was found to be adherent to the common carotid artery, 3·5 cm. of this vessel was resected and after some mobilization a direct end-to-end anastomosis was performed. This patient lived for four-and-a-half years before he died from another cause.

THROMBO-ENDARTERECTOMY

This operation was first performed by dos Santos (1947) and later modified by Reboul and Laubry (1950). Several surgeons, including Leriche and Kunlin (1947), Fontaine and Hubinot (1950), Freeman and Gilfillan (1952), Forty (1952), Crafoord and Hiertonn (1952), Wylie (1952), Luke (1954), and Wylie and Gardener (1955) have recorded their experience with this operation. The report of Reboul and Laubry states that, of 93 operations, 44 (47 per cent) remained patent, 38 (41 per cent) clotted again, and 11 (12 per cent) patients died. In our hands the results have been disappointing and approximate to those reported by Reboul and Laubry. Nevertheless we have not entirely abandoned the operation and consider that an occasional case is suitable.

The operation performed by removing the thrombus from the artery through a plane of cleavage in the tunica media was the first attempt to restore the blood-flow through a thrombosed artery. The best results are obtained with localized occlusions of large vessels such as the aorta or iliac arteries, but some idea of the strictness of the criteria which we apply when selecting patients for the operation of thrombo-endarterectomy may be obtained by stating that we have only performed it on 13 occasions since 1950, but 12 of these patients have patent vessels to-day.

EMBOLECTOMY

This operation will only be briefly mentioned, as Jepson (1955) has recently reviewed this subject. It is rarely needed in the upper limb; the collateral circulation here is so efficient that with proper conservative measures the pulse often returns to the wrist within forty-eight hours of a brachial embolus. On the other hand, embolic obstruction of the bifurcation of the abdominal aorta is best treated

by immediate operation, as are many embolic obstructions of the popliteal or common femoral arteries. Here a great deal depends upon the appearance of the limb; in many patients the blood-flow is returning by the time the patient reaches hospital, and conservative treatment (Rob, 1955 a) with anticoagulants and reflex vasodilatation proves to be sufficient. However, where good facilities are available popliteal or femoral embolectomy usually pays, for by this means a normal blood-flow can be restored. The first successful removal of a saddle embolus from the aortic bifurcation was performed by Bauer of Malmö, Sweden, in 1913.

AN AUTOGENOUS VEIN GRAFT

This operation was performed experimentally by Carrel and Guthrie (1905), and for the first time in patients by Lexer. By 1913 Lexer was able to report that he had resected three aneurysms of large peripheral arteries and restored continuity with an autogenous vein graft in each case. Two patients were alive and well with patent grafts; one died six days after the operation but the graft was found to be patent and intact. In Britain, Pringle in 1913 recorded two cases of aneurysms treated in this way. One patient worked for over three years after the operation and when he died of heart disease examination of the graft showed it to be patent, the other patient had a brachial aneurysm—he resumed full work as a blacksmith and a later investigation showed that he had been killed in 1916 fighting as an infantry soldier at Gallipoli.

During the Balkan War of 1912 and the Great War of 1914–18 many attempts were made to repair recent arterial wounds with autogenous vein grafts, but the results were unsatisfactory because of wound infections. On the other hand, many successes were obtained when vein grafts were used to bridge the gap after an arterial aneurysm had been excised. In 1925 Weglowski reported his follow-up of 51 patients operated on during the 1914–18 war; in each case an arterial aneurysm had been excised and an autogenous vein graft inserted. In 40 of these cases there was clear evidence that the graft was patent. In the Second World War few successes were obtained, but in the Korean War the successful use of vein grafts was extended to include some patients with recent wounds. The combined results reported by Jahnke and Seeley (1953) and Hughes (1954) from the U.S. Army Medical Corps in Korea show that in all 104 repairs of major arteries were performed for recent wounds; 79 (76 per cent) were repaired by a direct end-to-end anastomosis, 6 (5·8 per cent) by lateral suture, 15 (14·4 per cent) by an autogenous vein graft, and 4 (3·8 per cent) by a homologous arterial transplant. As a result of a later follow-up of 131 patients with a vascular repair performed on account of a wound, recent or old, inflicted during the Korean War, Hughes (1955) concluded that the order of preference for methods of repair was direct anastomosis, autogenous vein graft, and homologous arterial transplant.

HOMOLOGOUS ARTERIAL TRANSPLANTS

An autogenous arterial graft would be better than a transplant, but unfortunately man has no spare large arteries and so homologous transplants have to be used. If it ever becomes possible to replace the human coronary artery then a vessel such as the internal mammary could be used as an autogenous graft. Sandblom, Muren, Norden, Idbohin, Sandegard, and Dahlback (1953) and Potts, Alburg, and Fischer (1953) have devised a method of creating wide autogenous arterial grafts from narrow vessels, and for short segments this should be an improvement on a homologous transplant.

Carrel (1908) formed an experimental blood-vessel bank and in 1912 was awarded the Nobel Prize for his work, but it was not until 1949 that an efficient artery bank was established by Gross, Bill, and Peirce for clinical use. An artery bank is essential if homologous arterial transplants are to be used routinely in clinical practice, and a variety of methods have been tried. The disadvantage of Carrel and Gross's method is that the arteries are kept at a temperature of 4° C. in a refrigerator and can only be stored for six weeks, but it has the advantage that the vessels are preserved in a viable state for four to six weeks. This has been established by tissue culture experiments and estimation of the oxygen consumption of such arterial segments using the Warburg technique (Hiertonn, 1952). An alternative is to preserve the vessels in the frozen state at a temperature of − 20° C. or less (Eastcott and Hufnagel, 1950; Deterling, Coleman, and Paishley, 1951). Vessels stored in this way can be kept indefinitely. We have experience of frozen storage of arteries, either in empty tubes or in 20 per cent glycerol saline, and the results have been satisfactory. Of 39 patients with such transplants inserted during the last five years, 3 are dead, 31 left hospital with patent arteries, 8 of whom have thrombosed later, and 5 thrombosed in hospital before discharge. As will be seen later, these results are similar to those obtained with preservation by freeze-drying. Because of the inconvenience of frozen storage we followed the lead of Marrangoni and Cecchini (1951) and investigated the possibilities of freeze-drying (Eastcott, Holt, Peacock, and Rob, 1954). Other authors have reported their experiences with this method, including Strong (1954), Hufnagel (1954), Creech, DeBakey, Cooley, and Self (1954), and Flewett, Zinneman, Oldfield, Shucksmith, and Dexter (1955). We have used it since 1953 in clinical practice and our results are that out of 60 freeze-dried arterial transplants in patients, 5 patients are dead, 9 transplants thrombosed in hospital, 46 patients left hospital with patent vessels, in whom 9 transplants have thrombosed later. These results show that the freeze-dried homologous arterial transplant is satisfactory for clinical use, and because of its convenience it may be considered to be the best method for preserving such tissues.

The donor should be young, preferably under thirty years of age, and he should not have suffered from a transmittable disease. In addition, the arteries should be normal on naked-eye inspection. Martin and Lynn (1952) have used a preserved stillborn infant's aorta for reconstructing the popliteal artery and comment upon the easy availability of this vessel, a considerable advantage where suitable donors are difficult to obtain. The original arterial banks depended upon a meticulous aseptic technique to ensure that the material was sterile. The vessels

were removed from the donor by performing a sterile post-mortem dissection using every possible precaution. We still prefer this aseptic technique, but several authors have devised methods of sterilizing contaminated arteries which have worked well in clinical practice. Levin and Larkin (1909) preserved vessels in formalin—this both sterilized and preserved the vessels, but the proteins were denatured and the results obtained with this technique have not equalled those of refrigeration, freezing, or freeze-drying. Merker and Gross (1951) used irradiation by cathode rays to sterilize contaminated vessels, but Hui, Zeifer, Deterling, Paishley, Humphreys, and Glenn (1952) found that calcification occurred in many of these grafts within a few months of insertion. A satisfactory method is to sterilize the arterial segments either with ethylene oxide and then to preserve them by freeze-drying. Hufnagel, Rabil, and Reid (1953) used liquid ethylene oxide before freeze-drying and Hallén (1955) introduced ethylene oxide vapour into the freeze-drying circuit to sterilize the arteries. In both cases care must be taken to avoid explosions. Ethylene oxide only slightly denatures the proteins, and grafts stored in this way have worked well in practice. An alternative method developed by Trafas, Carlson, Lo Grippo, and Lam (1954) and Szilagyi, Overhulse, and Lo Grippo (1954) is to use beta-proprio-lactone. This is as efficient and it has the advantage that it is not explosive.

Heterologous Arterial Transplants.—These were first successfully used by Carrel (1907) and have the advantage that they can be easily obtained, and if they worked as well as homologous transplants they would be preferable. However, this is not so and Creech, DeBakey, Self, and Halpert (1954), as a result of an experimental and clinical study, conclude that arterial heterografts preserved by freeze-drying or in formalin are unsatisfactory as vascular transplants.

The Fate of an Arterial Transplant.—An autogenous segment of artery acts as a true graft and is indistinguishable both macroscopically and microscopically from a normal vessel. A homologous transplant does not survive. It used to be thought that the tissues of the host grew in and gradually replaced the transplant; we now think that this does not happen in man (Rob, 1954 a). After nine months the intima has grown out from 1–2 cm. from the ends of the host artery. In the gap between this true intima the transplant is covered by collagen and fibrin, and the media and adventitia have died; but most of these layers have persisted as dead donor tissue with only a little replacement by the fibrous tissue of the host which surrounds the whole transplant. Lastly, the elastic laminæ remain. This means that a human arterial transplant more than 4 cm. long consists over its central portion of a layer of fibrin, two layers of dead and almost amorphous donor artery, the elastic laminæ, and a few capillary tufts and areas of fibrous tissue where the host tissues have grown in. The preservation of the elastic fibres is probably the main reason why homologous arterial transplants have proved successful in clinical practice. Sauvage and Harkins (1954) have studied the behaviour of various types of vascular transplants inserted into the aortas of 148 young growing pigs. They conclude that fresh aortic autografts resemble the aorta of the host in all obvious respects both grossly and microscopically, and that they increase in calibre at essentially the same rate as the aorta of the growing host, that homologous aortic transplants, fresh or preserved, usually increase in calibre but at a slower rate than the aorta of the host, and that venous autografts inserted into the aorta, except for fibrous thickening, did not come to resemble the histological structure of an artery, and that they increased in calibre at a rate greater frequently than that of the aorta of the host. Recently Coleman, Deterling, and Paishley (1955) have studied eighteen homologous arterial transplants removed from dogs up to four-and-a-half years after implantation. They were functioning excellently, and there were no aneurysms but there was marked degeneration of the elastic fibres, and they raise again the unanswered question as to whether aneurysms will form or not.

PLASTIC AND OTHER ARTIFICIAL PROTHESES

Because a homologous arterial transplant does not act as a true graft a suitable artificial prosthesis should serve as well. The prosthesis may take the form of either a rigid or a pliable tube. The rigid tubes have been made of a great variety of materials, including glass, silver, aluminium, stainless steel, vitallium, polyethylene, nylon, and methyl methacrylate. Some of these tubes have been lined by autogenous or homologous vein segments and others have been used without any such cover, but the results on the whole have been unsatisfactory, and to-day the only use for such a prosthesis is to carry a valve, as recommended by Hufnagel, Rabil, Harvey, and McDermott (1954) for the treatment of aortic insufficiency. On the other hand, tubes made of pliable materials have given good results in both man and experimental animals. The first successful use of a material of this type was by Voorhees, Jaretzki, and Blakemore (1952). They used vinyon N. cloth (vinyl chloride—acrylonitrile) and by Blakemore and Voorhees (1954) were able to report that they had used this material in eighteen patients with satisfactory results. More recently a variety of other plastic cloths has been used, notably, nylon (a superpolyamide), orlon (an acrylic fibre), terylene (a polyester) and a multilayered cloth of nylon and polythene (Shumacker and King, 1954). Of these, it appears that terylene and orlon are the best. The use of orlon was pioneered by Hufnagel, and in 1955 he published the results of his experimental and clinical work. He had inserted an orlon prosthesis into fifteen patients over a period of sixteen months with good results. In Britain, Kinmonth, Taylor, and Lee (1955) have also found it satisfactory. Deterling and Bhonslay (1955) on the other hand prefer terylene. We have used a prosthesis of plastic cloth on 19 occasions in patients for the reconstruction of the aorta. Five are dead—2 from coronary occlusion and the others, who had leaking abdominal aneurysms, never recovered from the operation, the other 14 are alive and well. One who had a large aortic aneurysm lying within a tuberculous cold abscess was reported by us (Rob and Eastcott, 1955 a) in 1955 and is of interest because a homologous

arterial transplant would probably have ruptured because of the tuberculous infection whilst a plastic cloth prosthesis is working well one-and-a-half years later.

In spite of the successes obtained by ourselves and others with vinyon, orlon, nylon, and terylene cloths, we feel that they have definite disadvantages. They are not easy to suture in position, they may leak excessively, the seam may cause irregularities, they may contain added imperatics such as cyanide, and they are as yet not satisfactory for small vessels. Polyvinyl alcohol sponge prepared in the manner recommended by Shumway, Gliedman, and Lewis (1955) is, we think, better, and our results have been good enough to make us use this material in patients although Deterling (1955) reports rupture of the dog's thoracic aorta after reconstruction with this material. The advantages of polyvinyl alcohol sponge tubes are that they provide a smooth internal surface, can be fashioned to fit the aortic bifurcation, aortic arch or other special sites, they leak less than the plastic cloths, they are elastic, they are easy to suture to the host artery, and the material is readily available (Owen, 1955). To date we have inserted a prosthesis made of polyvinyl alcohol sponge into 21 patients and 15 are working satisfactorily.

FIG. 535.—This calcified aneurysm was associated with coarctation of the aorta. The patient was aged 26 and her symptoms were becoming increasingly severe. The aneurysm and coarctation were resected and continuity restored with a prosthesis of orlon cloth.

The search for a plastic prosthesis suitable for the reconstruction of vessels of the size of the human popliteal artery continues, and the best materials produced to date appear to be a crimped silicone-coated chemically-treated nylon tube (Edwards and Tapp, 1955) and polyvinyl alcohol sponge. The main disadvantage of this material is the difficulty of getting a dry suture line because it is hard to keep the suture tight enough, but five or ten minutes' pressure with a swab allows the leaks to stop, and the fact that it does not heal into the surrounding tissues in the way that polyvinyl sponge and the plastic cloths do.

INDICATIONS FOR ARTERIAL RECONSTRUCTION

These are increasing both in scope and frequency and may be grouped under the following several headings (Rob, 1954 b) :—

1. Congenital abnormalities.
2. Injuries :
   a. As a primary measure ;
   b. After a previous ligation.
3. Arteriovenous fistulas.
4. Aneurysms.

FIG. 536.—The prosthesis of orlon cloth bridging the defect left by resection of the aneurysm and the associated coarctation of the aorta shown in *Fig*. 535. This is functioning satisfactorily one year later.

5. After some emboli.
6. Occasionally in malignant disease.
7. In some patients with obliterative vascular disease :
   a. Primary thrombosis ;
   b. Thrombosis associated with arteriosclerosis.

1. Congenital Abnormalities.—The classical example of a congenital abnormality which can be corrected by an arterial reconstruction operation is coarctation of the aorta, and the first homologous arterial transplants used clinically were inserted by Gross and his colleagues (1949) for the correction of this abnormality. It has been stated that the usual reason why a coarctation of the aorta cannot be corrected by direct suture is the presence of a long stenosed segment. In our view this is not so, an associated aneurysm being a much commoner reason for the surgeon having to insert a vascular transplant or plastic prosthesis. In our own experience of 12 coarctations of the aorta repaired by an arterial transplant, 11 had an associated aneurysm, and in only 1 was the stenosed segment so long that a direct anastomosis was impossible on this account. *Fig*. 535 is a chest film showing a calcified aneurysm of the aorta just distal to a coarctation and *Fig*. 536 shows the orlon cloth prosthesis after it had been inserted to bridge the gap left by resection of the

coarctation and the associated aneurysm. These patients appear to do well and all 12 of ours are alive and well to-day.

2. Injuries.—

a. As a Primary Measure.—During the Balkan War of 1912 and the World Wars of 1914–18 and 1939–45 a few recent arterial injuries were repaired by direct suture or with the aid of an autogenous

FIG. 537.—This arteriogram was taken two weeks after two homologous arterial transplants had been inserted, one above and the other below the profunda femoris artery. The patient, a young butcher, accidentally stabbed himself twice in the groin; artery forceps applied as a first-aid measure crushed the vessel and direct suture was not possible.

vein graft, but their number must have been infinitesimal in relation to the total number of arterial wounds, and it was not until the recent Korean War that any large series of repairs of recent arterial wounds were reported. The results recorded by Jahnke and Seeley (1953) and Hughes (1954) for the United States army have already been quoted, and in addition Spencer and Grewe (1955) of the United States navy report a series of 97 arterial injuries, of which 42 were treated by direct suture, 44 with a homologous arterial transplant, 3 with a venous autograft, and 8 were ligatured.

In civilian practice vascular injuries are by no means uncommon, and we who have such patients referred to us have repaired 17 injured arteries during the last four years, 9 with a homologous arterial transplant, 3 with an autogenous vein graft, and 5 by a direct end-to-end anastomosis. Sixteen of these are patent, 1 has thrombosed, and this was due to a wound infection. This patient suffers from intermittent claudication, the others are symptom free. In our view, any injury to a major blood-vessel should be repaired if possible by a surgeon experienced in this type of work. It is well known that many limbs survive ligature of a major artery but many who escape gangrene are left with intermittent claudication or other symptoms due to a reduced blood-supply. *Fig.* 537 is an arteriogram from a young butcher who accidentally stabbed himself twice in the right groin. The femoral artery was divided both above and below

A B

FIG. 538.—In 1916 this patient's popliteal artery and vein were ligated for an arteriovenous fistula. In 1951 he developed intermittent claudication, and in 1953 the arteriogram on the left (A) was taken. A homologous arterial transplant was inserted and the result is shown in (B).

the profunda branch, and the fact that artery forceps had been applied as a first-aid measure made direct suture impossible. Two homologous arterial transplants were therefore inserted—one to the common femoral and the other to the superficial femoral arteries.

b. After a Previous Ligation.—When a major artery has been tied the reduced blood-flow, if it does not result in gangrene, may cause symptoms months or years later. On two occasions we have reconstructed an artery a considerable time after it had been tied. In 1916 a soldier developed a popliteal arteriovenous fistula following a gunshot wound. Three months later a quadruple ligation operation was performed at Birmingham; the result was excellent and he resumed full duty as a physical training instructor with the regular army. In 1951, thirty-five years after his popliteal artery had been tied, he developed intermittent claudication. This got steadily worse, and in 1953 his artery was reconstructed with a homologous arterial transplant (*Fig.* 538) (Rob and Eastcott, 1954 a). His vessel is patent to-day, but he suffers from mild intermittent claudication in the opposite calf due to arteriosclerosis.

3. Arteriovenous Fistulas.—The last case history shows that an arteriovenous fistula acts as an excellent stimulus to the formation of a collateral circulation. In this patient it was adequate for all

needs for more than thirty years after his popliteal artery had been tied. We strongly urge delay when possible before operating on these patients. After three months, operation is safer and the collateral circulation usually quite adequate. We also feel with equal conviction that a reconstruction operation is preferable to a quadruple ligation. In most patients it is possible to repair the artery of an arteriovenous

FIG. 539.—A femoral arteriovenous fistula which was excised and the artery and vein repaired by direct suture. Note the false sac and the filling of both artery and vein.

fistula by an end-to-end anastomosis, but sometimes an arterial transplant is required. In our series of 26 acquired arteriovenous fistulas seen since the end of the 1939–45 war, 12 have been treated by excision of the fistula and repair of both the artery and the vein, 6 involving small vessels were excised, 4 required a homologous arterial transplant to reconstruct the artery although the vein could be repaired by a direct anastomosis, and in 3 patients the artery was repaired by an end-to-end anastomosis but an autogenous graft was needed to restore the continuity of the vein. *Fig.* 539 shows a femoral arteriovenous fistula which was repaired, and *Fig.* 540 a large fistula involving the internal iliac artery and vein that was excised without reconstruction.

The first surgeon to use a vascular transplant for the repair of an arteriovenous fistula was Coenen (1913). He excised a femoral arteriovenous fistula and restored continuity of the artery with a saphenous vein autograft. In the two World Wars a number of vessels were reconstructed after the removal of an arteriovenous fistula and Makin's (1919) method of repairing the artery through the vein which he sacrificed was practised by many surgeons, but on the whole quadruple ligation with or without excision of the fistula was the method most widely used but the results, good as they were with respect to gangrene, were by no means perfect and Seeley, Hughes, and Jahnke (1952) report from the Korean War that in their series of arteriovenous fistulas quadruple ligation which was practised early in the series, although in no instance necessitating amputation, in about 30 per cent of patients produced definite symptoms of arterial insufficiency even when sympathectomy was employed as well. They

FIG. 540.—A large fistula between the internal iliac artery and vein. Note the dilatation of the proximal arteries including the common iliac and the aorta. This fistula was excised.

therefore adopted as a policy the repair of all major arterial lesions either by anastomosis or a transplant.

4. Aneurysms.—In civilian practice arterial aneurysms are usually arteriosclerotic or syphilitic in origin. Other causes include trauma, polyarteritis nodosa, and allied diseases, congenital weakness and infection producing a mycotic aneurysm. Any aneurysm which threatens life or causes sufficient symptoms should be excised and, if possible, the flow through the artery restored.

Aneurysms of the thoracic aorta are usually syphilitic and of the abdominal aorta arteriosclerotic in origin, and in spite of the fact that some patients survive for many years with such lesions the majority carry a very poor prognosis. In 1927 Colt collected the case histories of 624 patients with aortic aneurysms. He found that the average survival period from diagnosis was less than two years; 503 of these patients had thoracic aneurysms and 121 abdominal, 82 women lived on the average three months longer than 421 men, and he also noticed that the survival period was better in older than younger patients. These figures paint a very gloomy picture because the untreated prognosis is worse than that of

many tumours, and Colt excluded all dissecting aneurysms from his series. Estes (1950) in a review of 101 patients with abdominal aneurysms found that 50·8 per cent had died within three years and 33 per cent in less than one year from the date of diagnosis, and Cranley, Herrmann, and Preuninger (1954) from their analysis of 243 patients with aortic aneurysms, excluding 103 dissecting aneurysms, found that the aneurysm was the direct cause of death in 45 per cent and in an additional 10 per cent was the most probable cause of death. Eighty-two per cent of their aneurysms were syphilitic and 14 per cent arteriosclerotic. In view of this poor outlook many surgeons are treating these aneurysms by resection and reconstruction.

FIG. 541.—This large upper abdominal aneurysm was due to syphilis. The patient was aged 32 and suffered from severe root pains; the lower dorsal vertebral bodies were eroded and the aneurysm was pointing through the tenth intercostal space of the back. Under hypothermia it was resected and a homologous arterial transplant inserted. The patient died four months later from osteomyelitis of the spine and secondary hæmorrhage.

Swan, Maaske, Johnson, and Grover (1950), Lam and Aram (1951), Dubost, Allary, and Oeconomos (1952), DeBakey and Cooley (1953), Bahnson (1953), Brock (1953), Rob and Eastcott (1953), Rob (1954 a, b, c, 1955 a, b), and Moore and Telling (1955) have recorded their experiences with resection of aortic aneurysms and reconstruction with a homologous arterial transplant. By far the largest series is that collected by DeBakey, Cooley, and Creech (1955). They have resected over 200 aortic aneurysms, thromboses, and coarctations with very good results. In most of their patients continuity was restored with a homologous arterial transplant, but they have also used a large number of plastic prostheses including orlon cloth. Our own series now numbers 36 patients in whom an aortic aneurysm has been resected; 10 were repaired with a prosthesis of plastic cloth, 8 with a prosthesis of polyvinyl alcohol sponge and 18 with a homologous arterial transplant. Nine of these patients are dead, 3 were emergency operations (2 for leaking aneurysms and one for a dissecting aneurysm), 3 died from coronary occlusion, 1 died because a dissecting aneurysm formed in the arterial transplant,

FIG. 542.—The aortic transplant from the patient shown in *Fig.* 541. Note the appearance of the transplant and contrast it with that of the host aorta.

and 3 were very large aneurysms of the upper abdominal aorta, one of which did not survive the operation, one died three months later from osteomyelitis of the spine and the third is fit and well. The other 27 patients are fit and well. *Fig.* 541 is an aortogram from a patient who died four months after resection of the large upper abdominal aneurysm and reconstruction with a homologous arterial transplant. *Fig.* 542 shows the transplant after the patient's death.

Aneurysms of peripheral arteries, apart from those within the skull, rarely threaten life but they may cause severe symptoms. Gifford, Hines, and Janes (1953) report that 69 of their patients with 100 popliteal aneurysms between them developed before surgical treatment gangrene of the limb on 24 occasions. In 16 instances the aneurysm ruptured, 11 patients developed symptoms of pressure on nerves, and in 46 patients the aneurysm thrombosed or peripheral emboli occurred. As stated, Lexer (1913) was the first to resect a peripheral aneurysm and restore continuity with a blood-vessel transplant. He used an autogenous vein graft. Our experience, excluding military patients, consists of 18 homologous arterial transplants inserted after resection of a peripheral aneurysm and 6 reconstructions with

a plastic prosthesis (5 P.V.A. and one nylon) and 4 autogenous vein grafts. In addition we have restored continuity on 2 occasions by a direct end-to-end anastomosis after excision of an aneurysm of a peripheral artery. Fourteen of our aneurysms were on the femoral or popliteal arteries, 5 on the iliacs, and on 3 occasions another artery was involved. Seventeen of these vessels are patent to-day, one

FIG. 543.—Popliteal aneurysm in a patient with tabes dorsalis and a Charcot's joint. This had ruptured, producing a tense popliteal hæmatoma and ischæmia of the foot.

FIG. 544.—A post-operative arteriogram from the patient with the popliteal aneurysm shown in *Fig.* 543. A homologous arterial transplant has been inserted.

FIG. 545.—This patient had received 5000 r twelve years before for carcinoma of the iliac lymph-nodes. At operation the vessel was found to be grossly atherosclerotic and occluded to below the inguinal ligament.

FIG. 546.—The common and external iliac and most of the common femoral arteries of the patient shown in *Fig.* 545 have been reconstructed with a prosthesis of polyvinyl sponge.

tient died six months later from a coronary thrombosis and one with an iliac aneurysm died of intestinal obstruction in the immediate post-operative period, two vessels thrombosed—one in the immediate post-operative period probably due to a mild wound infection (neither is worse than they were before the operation), and in one patient with a mycotic aneurysm a severe secondary hæmorrhage necessitated an arterial ligation, but the limb has survived and he is awaiting

FIG. 547.

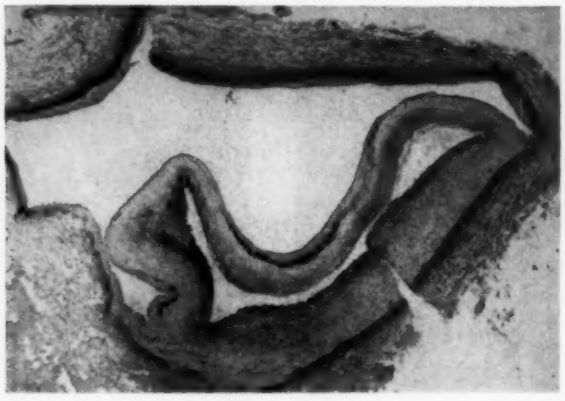


FIG. 548.

FIG. 547.—Primary thrombosis of the popliteal artery in a patient aged 25. His intermittent claudication distance was less than fifty yards. The cause was a cyst in the wall of the artery, illustrated in *Fig.* 548.

FIG. 548.—Photomicrograph of the cyst which lay within the wall of the popliteal artery illustrated in *Fig.* 547. Note the lumen of the cyst and the lumen of the artery. The contents of the cyst resembled the contents of a ganglion.

FIG. 549.—Continuity has been restored with a homologous arterial transplant after the cyst in *Fig.* 548 had been excised.

FIG. 549.

a graft when the wound has been soundly healed for some months. *Figs.* 543, 544 illustrate a popliteal aneurysm before and after operation. In one patient with a traumatic aneurysm of the bifurcation of the popliteal artery a reconstruction which included anastomosis of both the anterior and posterior tibial arteries has remained patent for over two years.

5. After some Emboli.—Embolic obstruction of the aortic bifurcation and many femoral and popliteal emboli are best treated surgically. Bauer of Malmö, Sweden, in 1913 was the first to remove successfully an embolus from the bifurcation of the abdominal aorta, and recently Burt, Learmonth, and Richards (1952), and Warren, Linton, and Scannell (1954) have recorded their experience with this operation. We believe that in selected patients aortic embolectomy may be attempted much later than was originally practised, and this view is shared by Warren, Linton, and Scannell (1954) and by Olwin, Dye, and Julian (1953). If the clinical features notify it and embolectomy is no longer possible, then it may be possible to restore the flow through the artery by means of a thrombo-endarterectomy or even with the aid of a vascular transplant.

6. Occasionally in Malignant Disease.—A malignant tumour which has invaded an artery is usually inoperable, but sometimes resection of a segment of a major blood-vessel completes a justifiable operation for cancer and makes a cure possible. As already described, we have one patient who lived for four-and-a-half years after such an operation and two others are well without evidence of recurrence, but their follow-up is still short. In each case a segment of the common carotid artery which was adherent to malignant lymph-nodes was resected and continuity restored with a homologous arterial transplant. Conley (1953) has reported a similar series of patients reconstructed with autogenous vein grafts. In addition a locally malignant lesion such as an adherent carotid body tumour is a clear-cut indication for a vascular reconstruction operation. *Figs.* 545, 546 are arteriograms from a patient whose common iliac artery thrombosed after a course of 5000 r to the iliac lymph-nodes and which was reconstructed with a tube of polyvinyl alcohol sponge.

7. Obliterative Vascular Disease.—

a. Primary Thrombosis.—This rare lesion which has been described by Learmonth, Blackwood, and Richards (1944) and Boyd, Ratcliffe, Jepson, and James (1949) may be defined as thrombosis of a major artery without any obvious cause and without evidence of arteriosclerosis in the occluded vessel. It is important to distinguish this lesion from the very common thrombosis which occurs in patients with arteriosclerotic vessels. The most usual artery to be involved is the popliteal but other major vessels may be affected. Our series consists of 12 patients with this lesion—an unduly large number, but such patients are referred to us for reconstruction operations and of these, 8 involved the popliteal

artery. The predominance of the popliteal artery may be due to the artery being subjected to repeated minor injuries as it passes through the adductor hiatus and behind the knee-joint, but another factor is that occlusion of this vessel produces major symptoms whilst a similar occlusion in the upper limb might pass almost unnoticed. We have operated on all 12 of our patients, and in each case restored continuity with a homologous arterial transplant. Nine of these are patent, the longest five years after his operation, and the 3 which have thrombosed appear to be no worse when compared with their pre-operative state. One patient is of particular interest; he thrombosed his popliteal artery at the age of twenty-five and a pre-operative arteriogram (*Fig.* 547) confirmed that the artery was occluded. As his walking distance before the onset of intermittent claudication was less than fifty yards, he was operated on. The popliteal artery presented a most unusual appearance and was found to consist of a cyst, measuring about 2 cm. in length and about 1 cm. in diameter, lying in the wall of the artery and occluding the lumen. The cyst contained a gelatinous material similar to that found in a ganglion; this was analysed and consisted of a mucoprotein of high viscosity. The diseased segment of artery was resected and the pathologist's report read as follows: "The specimen consisted of a segment of artery, in the wall of which was a fusiform cystic swelling containing clear yellow mucus. The cyst lay in the adventitia and was lined by flattened cells. There was a diminution in the elastic fibres in that half of the circumference of the artery in relation to the cyst." *Fig.* 548 is a photomicrograph of a section across the cyst and the artery, and *Fig.* 549 an arteriogram after a homologous arterial transplant had been inserted. A similar case was described by Hiertonn in 1954.

b. Arteriosclerotic Thrombosis.—The majority of patients on first developing symptoms from arteriosclerosis have a localized thrombosis of one or more main or important arteries. These are frequently anatomically suitable for direct surgery with the aim of restoring the blood-flow through the occluded vessel, but it must be remembered that arteriosclerosis is a general disease, and that many of the patient's arteries may be involved. There is no purpose in relieving intermittent claudication if angina pectoris substitutes a worse limit to the patient's activities. Kekwick (1951) found that, of 45 patients with intermittent claudication, 9 had angina pectoris, 5 had a past history of cardiac infarction, and 3 had suffered cerebrovascular accidents. Arteriosclerosis must be localized to an unusual degree to justify direct surgery. Selection is the key to success; for selection we rely mainly on the patient's age and family history, the appearance of the retinal arteries and the electrocardiogram, the size of the vessel which has thrombosed and the state of the patent vessel proximal and distal as seen on an arteriogram, and above all upon the extent of the disability which it has produced. As a general rule, young patients with major symptoms from occlusion of a large vessel and with little or no evidence of arteriosclerosis do well; in other patients one usually gets a good initial result but other vessels soon thrombose and symptoms recur.

FIG. 550.—This patient was aged 39. The aortic occlusion is level with the left renal artery. She was hypertensive, had red blood-cells and casts in her urine, and could only walk ten yards before the onset of pain.

FIG. 551.—Under hypothermia a homologous arterial transplant was inserted into the patient, whose arteriogram is shown in *Fig.* 550. She now does a full day's work as a housewife.

Table I gives the results of a follow-up of eighty-ive of our patients who have had a direct surgical peration (thrombo-endarterectomy, arterial trans-lant, vein graft or reconstruction with a plastic

Table I.—EIGHTY-FIVE ARTERIAL RECONSTRUCTIONS IN PATIENTS WITH OCCLUSIVE ARTERIAL DISEASE

Vessel	*No. of Recon-structions*	*Thrombosed in Hospital*	*Thrombosed Later*	*Patent To-day*
orta and Iliacs	28 (2 died in hospital)	1	1	24
emorals	37	11	8 (plus 1 dead since discharge)	17
opliteals	15	1	5	9
)thers	5	2	2	1

3 have thrombosed another artery since operation.

rosthesis) for the relief of symptoms due to obliterative arterial disease.

It will be seen that in our hands the best results have been obtained with the large vessels such as the aorta, and in our view occlusion of the aortic bifurcation is an important reason for reconstruction operation, but the popliteal results have also been satisfactory.

(1954 a), Julian, Grove, Dye, Javid, and Sadove (1954), Szilagyi and Overhulse (1955) and Rob (1955 b). As stated in *Table I* we have reconstructed the lower aorta or the iliac arteries on twenty-eight occasions in patients with obliterative vascular disease. In most cases we have used a homologous arterial transplant, but recently we have been using

FIG. 552.—An aortogram from a patient aged 34 with gangrene of the right foot. A lumbar ganglionectomy had been performed three years before. *Fig.* 553 shows the foot before and after reconstruction of the aortic bifurcation with a plastic prosthesis.

FIG. 553.—The feet of the patient whose aortogram is shown in *Fig.* 552 before and four weeks after reconstruction of the aorta with a plastic prosthesis.

OCCLUSIVE DISEASE OF THE AORTA AND ILIAC ARTERIES

This lesion which is mentioned in Allbutt and Roleston's (1909) System of Medicine was described in 1923 and again in 1940 by Leriche when he gave the first detailed description of the syndrome of thrombosis of the bifurcation of the abdominal aorta. He treated this lesion by resection of the diseased segment and a bilateral sympathetic ganglionectomy, a procedure also practised by others including Adams-Ray (1954) with good initial results. The first surgeon to reconstruct the aortic bifurcation after resection of the thrombosed segment was Oudot (1951) and he used a homologous arterial transplant. Since then good results with this operation have been reported by DeBakey and Cooley an increasing number of plastic prostheses. In addition it is in this region that thrombo-endarterectomy gives the best results as reported by Forty (1952), Crafoord and Hiertonn (1952), Rob and Eastcott (1953), Luke (1954), Bogardus, Beretta, Huff, and Payne (1954), and Wylie and Gardener (1955).

The danger of an aortic thrombosis is that it may spread up and involve the renal arteries. We have seen this on two occasions, and the literature contains reports of many others (Johnson, 1954). Such high occlusions are in urgent need of surgery, and are best operated on under hypothermia as the aortic clamp has to be applied above the renal arteries. *Figs.* 550, 551 illustrate a high thrombosis of the abdominal aorta which developed in a woman aged 39 years. Her claudication distance was about

ten yards ; she had hypertension and red blood-cells and casts in her urine. At operation under hypothermia fresh clot was found in the left renal artery ; a homologous arterial transplant was inserted, and the patient is fit and well with a normal blood-pressure, and capable of a full day's work two-and-a-half years later.

Figs. 552, 553 illustrate reconstruction of the aorta for gangrene. This patient, aged 34, had a bilateral lumbar ganglionectomy four years before and an above-knee amputation was considered, but the aortogram, *Fig.* 552, showed a lesion suitable for a reconstruction operation. This was carried out using a plastic prosthesis, and *Fig.* 553 shows the foot before and four weeks after this operation ; all four ankle pulses are palpable and the patient can walk well.

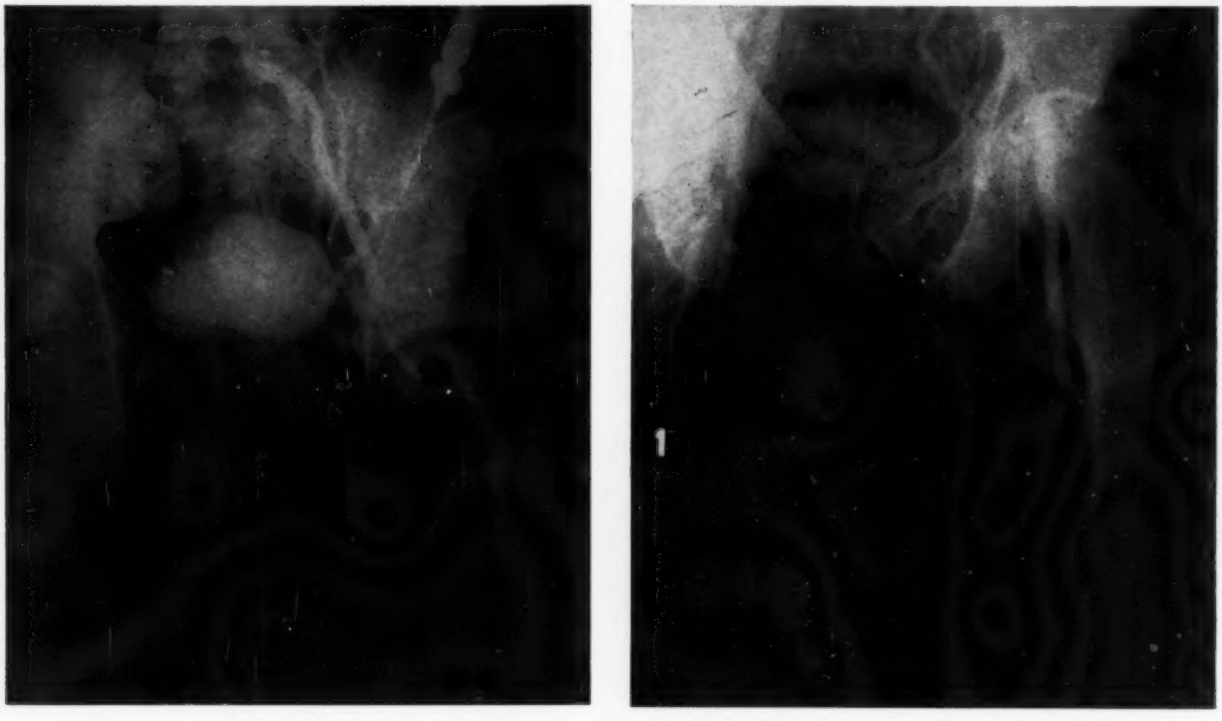


FIG. 554.—Occlusion of the common femoral artery. A by-pass end-to-side proximal anastomosis and end-to-end distal anastomosis has been inserted.

OCCLUSIVE DISEASE OF THE FEMORAL AND POPLITEAL ARTERIES

Table I shows that in our series occlusions of the popliteal artery have done better when treated by a reconstruction operation than have occlusions of the femoral artery. The reason for this we think is that a short thrombosis of the superficial femoral artery of a young patient may produce relatively few symptoms, whilst a similar occlusion in the popliteal artery may be crippling. This means that a femoral thrombosis by the time it is reconstructed often does badly because the host vessel is too diseased, whilst the less degenerate popliteal artery does better. This does not mean that we are against direct surgery for femoral thrombosis ; all it means is that selection must be very strict. It has been stated on numerous occasions that thrombosis in a reconstructed artery may lead to gangrene ; in our experience this is no so, and in no patient of ours has gangrene or amputation followed a reconstruction operation unless established gangrene before operation or severe rest pain was the reason for attempting to restore the blood-flow.

For vessels of this size thrombo-endarterectomy is not very satisfactory, and better results follow some form of vascular transplant. The surgeons of France, notably Fontaine and Hubinot and their colleagues (1950, 1951, and 1952), and Julian, Grove, Dye, Olwin, and Sadove (1953) from the U.S.A. have considerable experience with resection of the occluded segment and its replacement by an autogenous vein graft. We have preferred a homologous arterial transplant for a similar procedure. Eastcott (1953) and many other surgeons including Szilagyi and Overhulse (1955), Shaw and Wheelock (1955), and Horton (1955) have also used them. Horton considers that reconstruction of the femoral artery for atheroma is only occasionally worthwhile.

An alternative and perhaps a better procedure is to insert a by-pass around the occluded segment. This was first performed by Kunlin (1949) using an autogenous vein graft anastomosed end-to-side above and below the block, but the results were not particularly good. Recently this method has been tried again, but using homologous arterial transplants, by Cockett and by Linton (1955 a, b) and Crawford and De Bakey (1955) and the results have been much better. Linton (1955 a, b) has kindly sent me the figures of his great personal experience with the end-to-side technique and the accompanying *Table II* gives his immediate results and shows what an outstanding success it has been. In Britain Cockett

(1955) inserted his first by-pass graft in 1953 and since then he has used the method on 10 patients out of a total of 30 arterial transplants. His results in these 10 patients are one death, 5 occlusions from various causes and 4 patent grafts to-day. He has used the method as an alternative to amputation in several elderly patients and, knowing the type of material with which he has worked, we feel that these

FIG. 555.—The carotid bifurcation resected from a woman aged 66 who suffered from intermittent attacks of right hemiparesis and blindness of the left eye. Resection and reconstruction by a direct anastomosis between the common and internal carotid arteries have prevented further attacks.

results are very good. The method has many advantages, including the fact that the operation is easier and less severe. We have used it on a number of occasions, and *Fig.* 554 shows arteriograms illustrating the method. In addition, Kinmonth,

Table II.—COMPARISON OF IMMEDIATE THROMBOSIS WITH (A) END-TO-END ANASTOMOSES, (B) END-TO-SIDE ANASTOMOSES FROZEN IRRADIATED ARTERIAL HOMOGRAPHS

Artery	*End-to-end* Total No.	*End-to-end* No. of Thromboses	*End-to-side* Total No.	*End-to-side* No. of Thromboses
Common Iliac	14	4 (29 per cent)	1	0
External Iliac	7	16 (14 per cent)	67	1 (1·5 per cent)
Femoral	22	5 (23 per cent)	31	0
Popliteal	23	6 (26 per cent)	37	1 (3 per cent)
Total	66	16 (24 per cent)	136	2 (1·5 per cent)

(*Provided by R. R. Linton of the Massachusetts General Hospital, Boston.*)

Taylor, and Lee (1955) report the use of a side-to-side technique using a plastic cloth prosthesis; they stress that an important feature is that there must be a complete block in the affected vessel.

The length of vessel which may be reconstructed is of interest. Our longest is from the level of the renal arteries to the common femoral, but Linton (1954) reports the successful insertion of a 45 cm. homologous arterial transplant from the aortic bifurcation to the popliteal artery.

OCCLUSIVE DISEASE OF OTHER ARTERIES

The main interest here is the coronary artery but, in spite of much work, no real progress has been

FIG. 556.—Pre-operative carotid arteriogram showing the localized partial occlusion of the internal carotid artery illustrated in *Fig.* 555.

made in the direct reconstruction of this vessel after a coronary thrombosis. The *carotid artery*, however, presents a more encouraging picture. The syndrome of internal carotid thrombosis was recognized by Chiari (1905) and Hunt (1914) and now, following the introduction of carotid arteriography by Moniz (1927), it is being diagnosed with increasing frequency. As yet there is no adequate treatment for established occlusion of this artery, but fortunately prodromal symptoms may occur (Millikan and Siekert 1955) and make the diagnosis possible before the complete and irrevocable occlusion has occurred. Chambers (1954) and Millikan and Siekert (1955) advise anticoagulant therapy for these patients with a prethrombotic lesion, but from an anatomical study of the lesion we feel that the best prospect of cure is with a direct surgical operation. The prethrombotic lesion is a plaque of atheroma at the junction of the common and internal carotid arteries (*Fig.* 555) often associated with complete occlusion of the external carotid artery at its origin and with relatively normal vessels above and below. This so narrows the internal carotid flow that intermittent attacks of headache, hemiparesis, unilateral blindness, and speech defects occur. Resection of

this abnormal segment of artery and reconstruction either with a direct anastomosis or a transplant is the treatment we advise. In 1954 Eastcott, Pickering, and Rob reported a successful result with this method in a woman, aged 66, and she is alive and well without having suffered from any further attacks of blindness or hemiplegia since resection of the diseased segment of artery and restoration of the blood-flow by a direct anastomosis between the common and internal carotid arteries one-and-a-half years ago. *Fig.* 556 shows her carotid arteriogram before the operation.

TECHNIQUE

The actual technique of vascular suture was worked out by Carrel (1907) and has not materially altered apart from the introduction by Kovanov of Moscow (1955) of a most ingenious method for mechanically suturing blood-vessels, which we have used with success and feel may well have an important place in the reconstruction of small vessels because of the perfect apposition which is achieved. We use 0000 paraffin dipped silk for the aorta and 00000 for smaller vessels ; two or three interrupted everting mattress sutures are inserted as guides and the anastomosis completed with a continuous over and over stitch. The technique which we employ has been described by Rob and Eastcott (1953), but we join with Linton (1954) in stressing that these operations are time-consuming—some may take as long as twelve hours—and great care is needed.

Clamps.—During recent years a large variety of blood-vessel clamps have been introduced, mostly for cardiac operations. In our view, many of these instruments are inferior to the older and simpler methods of occluding an artery. Rob and Henson (1956) have compared the relative merits of a number of clamps when used for the occlusion of a medium-sized artery, and in their opinion the tape tourniquet and bulldog clamp give the best results. When it is not possible to use either of these, a Pott's clamp is probably the best alternative. We use a tape tourniquet on the aorta and iliac vessels and also for smaller arteries, with the bulldog clamp as a good alternative in this instance. Sometimes it is difficult to apply the tape if only a short length of vessel can be mobilized. Under these circumstances we use a Pott's clamp. The tape tourniquet is applied by passing a wide tape round the artery, laying a piece of rubber tubing of approximately the same diameter as the artery on its long axis, tightening the tape until the vessel is occluded, and then applying a gall-bladder or other suitable clamp to the tape so that the artery is effectively clamped.

Exposure.—In most instances the artery is exposed in the usual way, but extension of vascular surgery to new sites has made new surgical approaches necessary. For example, the arch of the aorta can be satisfactorily reached through a transverse anterior thoracic incision which opens both pleural cavities and passes through the sternum at the level of the second intercostal space. Another relatively new exposure is that of the aorta above the renal arteries. Sometimes this is reached via a left thoraco-abdominal incision, the spleen and pancreas being carried forwards and the aorta and its branches exposed from their left antero-lateral surface. This route is not satisfactory when the reason for operating is a high thrombosis of the abdominal aorta. In these patients the aorta must be clamped above the renal arteries and the bifurcations of both common iliac arteries controlled. This exposure for a high thrombosis of the abdominal aorta has been described by Rob (1955 b). Another site which may cause difficulty is the femoro-popliteal junction ; this is best reached by laying the patient on his side with the bad leg nearest to the table and the good leg flexed fully at the hip.

Vein Grafts.—The difficulty here is to insert the graft under sufficient tension and to overcome the apparent disparity in size. It is also important that the vein should be reversed before it is placed in the artery so that the valves do not obstruct the arterial flow. Weglowski (1925), and Julian, Dye, Olwin, and Jordan (1952) have devised a neat method of avoiding these difficulties for use when the diseased artery and donor vein are adjacent. The internal saphenous vein is exposed in the same wound as the diseased femoral artery. It is divided at the distal end and the distal cut end of the vein turned up and anastomosed end-to-end or end-to-side to the artery proximal to the occlusion. The clamps are then removed and this temporary arteriovenous fistula allowed to function for a few minutes. This stretches the vein and makes certain that the surgeon has reversed it. The proximal end of the vein is now divided and the operation completed by anastomosing it to the artery distally. In our view autogenous vein grafts, unless inserted by a very experienced surgeon, give results which are inferior to those obtained with homologous arterial transplants (Rob and Eastcott, 1955 b), but this view is not shared by Linton (1955) who reports that 61 per cent of 13 autogenous vein grafts and 77 per cent of 68 homologous arterial transplants were successful. In spite of the higher failure of these grafts he feels that for replacement of the femoral artery a saphenous vein graft is preferable when the patient's vein is suitable for this purpose.

Thrombo-endarterectomy.—As stated, we reserve this operation for the occasional very favourable patient. The technique is to make a longitudinal incision into the artery where it is obstructed, remove the thrombus, making a careful blunt dissection in a plane of cleavage which develops in the media, and then to suture the incision in the artery. On the other hand, we often use the operation of thrombo-endarterectomy, particularly of the proximal stump, as an aid to an arterial transplant operation in a high occlusion of the abdominal aorta, but we feel that this may be dangerous at the distal end because of the risk of dissection deep to the atheromatous plaque. After the aorta has been clamped above the renal arteries it is divided and the clot removed from the proximal stump between the renal vessels and the line of the anastomosis. When the whole area is clear of clot the aortic clamp is released for a moment to prove that the vessels are patent ; this clamp is then reapplied and the aorta and renal arteries distal to the clamp washed out with saline. In our view, it is a mistake to admit blood to a segment which has been cleared by the operation of thrombo-endarterectomy before all

clamps can be removed and a free through flow maintained so that clotting in this segment is less likely to occur.

Leaking Aneurysms.—Rupture of an aortic aneurysm, particularly if it is into the extraperitoneal

FIG. 557.—Aortogram from a patient aged 42 whose aortic aneurysm had leaked extraperitoneally, producing a large hæmatoma containing approximately two litres of blood.

tissue planes, does not lead to the immediate death of the patient, and there is often time for adequate resuscitation before operation. The successful resection of leaking abdominal aneurysms has been reported by Bahnson (1954), Gerbode (1954), and DeBakey and Cooley (1954 b). We have treated five cases in this way and find that with adequate blood replacement operation can be successful. One of our patients travelled one hundred and fifty miles by ambulance and survived the operation for four weeks; he was the patient mentioned earlier who died a month later because a dissecting aneurysm formed in the arterial transplant. *Fig.* 557 is his preoperative aortogram.

Treatment of Arterial Injuries.—In 1940 Learmonth made the observation that intimal damage is greater than the external appearance of the artery would indicate, and he also stated that a transverse wound of an artery was often best treated by completing the division and performing an end-to-end anastomosis. A recent paper by Moore, Nyhus, Kanar, and Harkins (1954) reports experiments which support Learmonth's clinical conclusions; they report that the best treatment of a wound of a blood-vessel is resection of at least 3 mm. beyond the gross intimal defect followed by an end-to-end anastomosis.

Making Plastic Prostheses.—We prefer the methods devised by Hufnagel (1955) for making a plastic cloth prosthesis, and by Shumway, Gliedman, and Lewis (1955) and Owen (1955) for making a prosthesis of polyvinyl alcohol sponge. In brief, the cloth is cut with pinking shears to the required shape and sewn into a tube with a French seam using orlon, terylene, or nylon thread. The ends are turned back to make a cuff, the prosthesis is thoroughly washed

FIG. 558.—A prosthesis of polyvinyl sponge in position after resection of an abdominal aneurysm. This patient, who was aged 72, is alive and well with a satisfactory blood-flow to the lower limbs.

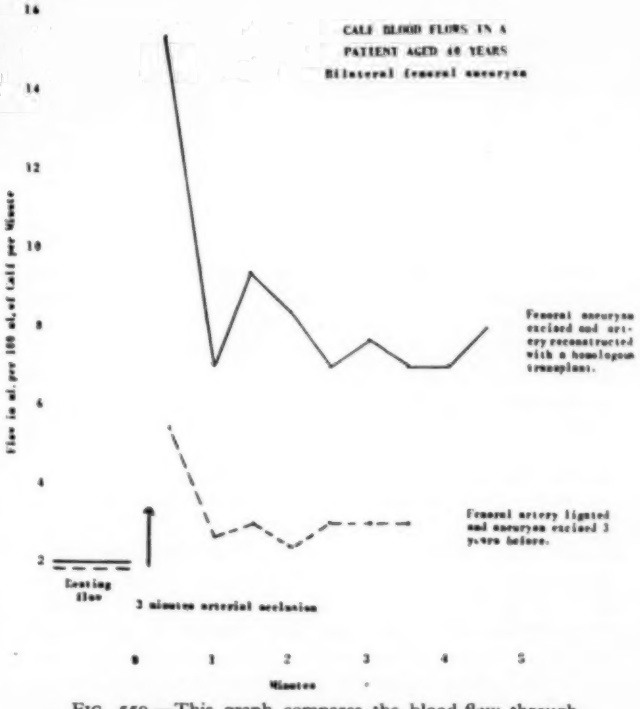

CALF BLOOD FLOWS IN A
PATIENT AGED 40 YEARS
Bilateral femoral aneurysm
Femoral aneurysm excised and artery reconstructed with a homologous transplant.
Femoral artery ligated and aneurysm excised 3 years before.
Resting flow
3 minutes arterial occlusion
Minutes

FIG. 559.—This graph compares the blood-flow through the calf after five minutes' arterial arrest in the limbs of a patient who had a femoral artery ligation on one limb and some years later a reconstruction operation on the opposite limb for a second femoral aneurysm. The result by this measurement is far better in the limb with an arterial reconstruction.

first with a detergent and then in water, finally after autoclaving it is ready for use and is sutured into the patient with a silk stitch in the same way as an arterial transplant. Polyvinyl sponge is cut into strips about 3 mm. thick, 3 cm. wide and of a convenient length. These are then washed in water and, whilst wet, wound on to a mould of the required shape, the sponge

being bound to the mould with a gauze bandage. It sets into a smooth-surfaced elastic tube which should be kept moist until used and sterilized by boiling on the mould. With suitable moulds a prosthesis of any shape or size can be constructed, including one to replace the arch of the aorta with its branches (*Fig.* 558).

Shunt Grafts.—These have been used by Clatworthy and Varco (1950), Schafer and Hardin better because it does not require a surgical operation to set it up, ventricular fibrillation appears to be less frequent, and it is simpler.

Hyperæmia.—When the clamp is released from a major artery there is a pronounced hyperæmia in those parts supplied by the artery. This and other of the circulatory changes which develop after the reconstruction of an obstructed femoral or popliteal

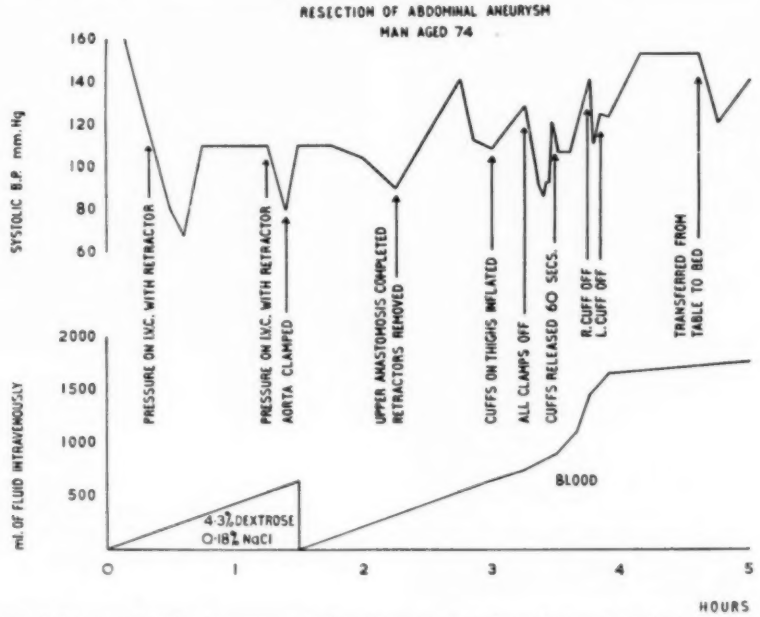


FIG. 560.—Graph of the systolic blood-pressure during the reconstruction of the abdominal aorta in a patient aged 70. Note the changes with pressure on the inferior vena cava, slow removal of the aortic clamp, and release of the blood-pressure cuffs of the thighs.

(1952), and Mahorner and Spencer (1954) to provide a temporary blood-flow whilst a major artery such as the thoracic aorta in a patient without coarctation of the aorta has been cross-clamped. In addition, Fryfogle, Small, Stenborg, and Samberg (1955) has devised a most ingenious method of inserting a vascular transplant using temporary split metal cuffs which are removed after the anastomoses have been completed. Using this technique it is possible to transplant the whole arch of the aorta of a dog in hypothermia time.

Hypothermia.—This is a useful aid when the blood-flow through a major artery to vital structures such as the brain, spinal cord, or kidneys has to be interrupted, whilst it is not yet known in man for how long the thoracic aorta in a patient without a coarctation can be clamped without permanent damage to the spinal cord. In one patient of ours cooled to 26° C., temporary changes in the neurological responses occurred after the aorta had been cross-clamped for two hours at the level of the ninth thoracic vertebra (Rob and Eastcott, 1954 b). Hypothermia was introduced as an aid to cardiovascular surgery by Bigelow, Callaghan, and Hopps (1950) who used external cooling, and others including Swan, Zeavin, Blount, and Virtue (1953), Churchill Davidson, McMillan, Melrose, and Lynn (1953), and Pontius, Brockman, Hardy, Cooley, and DeBakey (1954) have published their experiences with the method. An alternative method, blood-stream cooling, has been used by Delorme (1952) and by Brock and Ross (1955). We feel that surface cooling is artery have been investigated by Eastcott, Snell, and Hamilton (1956) (*Fig.* 559). Of importance are the great changes in circulatory mechanics which occur when the clamp is removed from the aorta of patients either with or without a previous coarctation, but particularly the latter. These have been investigated by Cooper and Kenyon (1955) of our hospital. When the clamps are removed there is a sudden drop in blood-pressure, and this may prove fatal probably from relative coronary ischæmia. This may be controlled by gradual or intermittent release of the aortic clamp and by massive blood transfusion. Cooper and Kenyon have shown that this is due to hyperæmia in the area rendered ischæmic by the aortic clamp and to refilling of the vascular bed. They advise the temporary arrest of the circulation to the lower limbs by blood-pressure cuffs applied to the thighs and inflated to a level above that of the systolic blood-pressure, but of course they must not remain inflated for more than about twenty minutes. *Fig.* 560 is a graph showing the changes in blood-pressure during such an operation.

Anticoagulants.—At one time we used heparin in the immediate post-operative period for transplants of peripheral arteries and, to prevent the troublesome complication of a wound hæmatoma, we left the wounds open and closed them on the fourth post-operative day by the operation of delayed primary suture (Rob, 1953), but as our technique improved we reserved this for patients with an arteriosclerotic thrombosis and then abandoned it altogether. We

have used no heparin during the immediate postoperative period for any of our last fifty arterial reconstructions, although we use it locally during the operation in many patients.

On the other hand, we are using anticoagulants to an increasing extent for the prevention of further thrombosis in patients with an arteriosclerotic thrombosis because, not only may these patients thrombose again the arteries in the limb which has been reconstructed, but they may thrombose a coronary or cerebral vessel. As yet there is no proof, but there is an accumulating volume of evidence that long-term anticoagulant therapy may prevent at least some of these thromboses (*Lancet* Editorial, 1954; Olwin and Friedman, 1954). We have used indevan (phenylindandione) for this purpose and kept it up for as long as three years, but it is only suitable for intelligent patients.

SUMMARY AND CONCLUSIONS

1. We have reviewed the literature of arterial reconstruction and selected certain aspects of this subject for discussion. Where possible we have drawn conclusions from our own experience and our own results have been quoted.

2. An artery may be reconstructed by a direct repair or anastomosis, the operations of embolectomy or thrombo-endarterectomy, an autogenous vein graft, a homologous arterial transplant, or with a plastic prosthesis. Under certain circumstances an autogenous arterial graft can be used, and a few surgeons have used heterologous arterial transplants.

3. For reconstruction of the aorta or one of its large branches in a body cavity we prefer a plastic prosthesis, the operation of thrombo-endarterectomy, or a homologous arterial transplant with a growing preference for the former. For reconstruction of peripheral arteries we prefer a homologous arterial transplant, but feel that the autogenous vein graft in experienced hands may give better long-term results particularly in patients who do not suffer from atherosclerosis. We have great hopes that a satisfactory plastic prosthesis will soon be found for these smaller vessels.

4. Of the various plastic prostheses for use in the aorta we prefer polyvinyl alcohol sponge tubes to plastic cloths, but of the cloths we have found orlon and terylene satisfactory.

5. We have experience in patients of 194 arterial reconstruction operations comprising; 99 homologous arterial transplants, 17 autogenous vein grafts, 19 reconstructions with a prosthesis of plastic cloth, 21 reconstructions with a prosthesis of polyvinyl alcohol sponge, 13 thrombo-endarterectomies, and at least 25 direct arterial repairs. It is upon this that our conclusions have been based.

REFERENCES

ADAMS-RAY, J. (1954), *Acta oto-laryng., Stockh.*, **116**, Suppl. p. 7.
ALLBUTT, C., and ROLESTON, H. D. (1909), *System of Medicine*, **6**, 809. London: Macmillan.
BAHNSON, H. T. (1953), *Ann. Surg.*, **138**, 377.
— — (1954), *Circulation*, **9**, 494.
BAUER, F. (1913), *Zbl. Chir.*, **40**, 1945.
BIGELOW, W. G., CALLAGHAN, J. H., and HOPPS, J. A. (1950), *Ann. Surg.*, **132**, 531.
BLAKEMORE, A. H., and VOORHEES, A. B. (1954), *Ibid.*, **140**, 324.
BOGARDUS, G. M., BERETTA, F. F., HUFF, R. L., and PAYNE, J. T. (1954), *Arch. Surg., Chicago*, **68**, 222.
BOYD, A. M., RATCLIFFE, A. H., JEPSON, R. P., and JAMES, G. W. H. (1949), *J. Bone Jt Surg.*, **31-B**, 325.
BROCK, R. C. (1953), *Proc. R. Soc. Med.*, **46**, 119.
— — and ROSS, D. H. (1955), *Guy's Hosp. Rep.*, **104**, 99.
BURT, C. C., LEARMONTH, J., and RICHARDS, R. L. (1952), *Edinb. med. J.*, **59**, 65.
CARREL, A. (1904), *Bull. Johns Hopk. Hosp.*, **18**, 18.
— — (1907), *J. exp. Med.*, **9**, 226.
— — (1908), *J. Amer. med. Ass.*, **51**, 1662.
— — and GUTHRIE, C. C. (1905), *Ann. Méd.*, **10**, 1101.
CHAMBERS, W. R. (1954), *Surgery*, **36**, 980.
CHIARI, H. (1905), *Verh. dtsch. path. Ges.*, **9**, 326.
CHURCHILL-DAVIDSON, H. C., MCMILLAN, I. K. R., MELROSE, D. G., and LYNN, R. B. (1953), *Lancet*, **2**, 1011.
CLATWORTHY, H. W., and VARCO, R. L. (1950), *Proc. Soc. exp. Biol., N.Y.*, **74**, 434.
COCKETT, F. B. (1955), Personal communication.
COENEN, F. (1913), *Verh. dtsch. Ges. Chir.*, **42**, 115.
COLEMAN, C. C., DETERLING, R. A., and PAISHLEY, M. S. (1955), *Surgery*, **37**, 64.
COLT, C. H. (1927), *Quart. J. Med.*, **20**, 331.
CONLEY, J. J. (1953), *Ann. Surg.*, **137**, 205.
COOPER, K. E., and KENYON, J. R. (1955), Paper read at Meeting of the Physiological Society, Dundee.
CRAFOORD, C., and HIERTONN, I. (1952), *Acta chir. scand.*, **104**, 81.
CRANLEY, J. J., HERRMANN, L. G., and PREUNINGER, R. M. (1954), *Arch. Surg., Chicago*, **69**, 185.
CRAWFORD, E. S., and DEBAKEY, M. E. (1955), *Surg. Gynec. Obstet.*, **101**, 529.
CREECH, O., DEBAKEY, M. E., COOLEY, D. A., and SELF, M. M. (1954), *Ann. Surg.*, **140**, 35.
— — — — SELF, M. M., and HALPERT, B. (1954), *Surgery*, **36**, 431.
DEBAKEY, M. E., and COOLEY, D. A. (1953), *J. Amer. med. Ass.*, **152**, 673.
— — — — (1954 a), *Ann. Surg.*, **139**, 763.
— — — — (1954 b), *Post Grad. med. J.*, **16**, 334.
— — — — and CREECH, O. (1955), *Symposium on Cardiovascular Surgery, Henry Ford Hospital*, 468. Philadelphia: W. B. Saunders Co.
DELORME, E. J. (1952), *Lancet*, **2**, 914.
DETERLING, R. A. (1955), *Surgery*, **38**, 91. (During discussion of his paper.)
— — and BHONSLAY, S. B. (1955), *Ibid.*, **38**, 71.
— — COLEMAN, C. C., and PAISHLEY, M. S. (1951), *Ibid.*, **29**, 419.
DOS SANTOS, J. C. (1947), *Mém. Acad. Chir.*, **73**, 409.
DUBOST, C., ALLARY, M., and ŒCONOMOS, N. (1952), *Arch. Surg., Chicago*, **64**, 405.
EASTCOTT, H. H. G. (1953), *Ann. R. Coll. Surg., Engl.*, **13**, 177.
— — HOLT, L. B., PEACOCK, J. H., and ROB, C. G. (1954), *Lancet*, **1**, 1311.
— — and HUFNAGEL, C. A. (1950), *Amer. Coll. Surg., Surg. Forum*, 269.
— — PICKERING, G. W., and ROB, C. G. (1954), *Lancet*, **2**, 994.
— — SNELL, E., and HAMILTON, M. (1956), *Clin. Sci.* Accepted for publication.
EDITORIAL (1954), *Lancet*, **2**, 742.
EDWARDS, W. S., and TAPP, J. S. (1955), *Surgery*, **38**, 61.
ESTES, J. E. (1950), *Circulation*, **2**, 258.
FLEWETT, J. H., ZINNEMAN, K. S., OLDFIELD, M. W. C., SHUCKSMITH, H. S., and DEXTER, F. (1955), *Lancet*, **1**, 888.
FONTAINE, R., BUCK, P., RIVEAUX, R., KIM, M., and HUBINOT, J. (1951), *Lyon chir.*, **46**, 73.

FONTAINE, R., and HUBINOT, J. (1950), *Acta chir. belg.*, **49**, 580.
— — RIVEAUX, R., KIM, M., and KEY, R. (1952), *Proc. Congr. europ. surg. Soc.*, 227.
FORTY, F. (1952), *Brit. med. J.*, **2**, 264.
FREEMAN, N. E., and GILFILLAN, R. S. (1952), *Surgery*, **31**, 115.
FRYFOGLE, J. D., SMALL, J. T., STENBORG, W., and SAMBERG, C. (1955), *Symposium on Cardiovascular Surgery, Henry Ford Hospital*, 476. Philadelphia: W. B. Saunders Co.
GERBODE, F. (1954), *Surg. Gynec. Obstet.*, **98**, 759.
GIFFORD, R. W., HINES, E. A., and JANES, J. M. (1953), *Surgery*, **33**, 284.
GROSS, R. E., BILL, A. H., and PEIRCE, E. C. (1949), *Surg. Gynec. Obstet.*, **88**, 689.
HALLÉN, L. G. (1955), *Acta chir. scand.*, **204**, Suppl.
HIERTONN, T. (1952), *Acta orth. scand.*, **10**, Suppl.
— — (1954), *Nord méd.*, **51**, 535.
HÖPFNER, E. (1903), *Arch. klin. Chir.*, **71**, 417.
HORTON, R. (1955), *Brit. med. J.*, **1**, 81.
HUFNAGEL, C. A. (1954), *Ciba Foundation Symposium on the Preservation and Transplantation of Normal Tissues, London*, 196. London: Churchill.
— — (1955), *Surgery*, **37**, 165.
— — RABIL, P. J., HARVEY, W. P., and MCDERMOTT, T. F. (1954), *Ibid.*, **35**, 673.
— — — — REID, L. (1953), *Amer. Coll. Surg., Surg. Forum*, 162.
HUGHES, C. W. (1954), *Surg. Gynec. Obstet.*, **99**, 91.
— — (1955), *Ann. Surg.*, **141**, 297.
HUI, K. K. L., KEIFER, E. B. C., DETERLING, R. A., PAISHLEY, M. S., HUMPHREYS, G. H., and GLENN, F. (1952), *Amer. Coll. Surg., Surg. Forum*, 255.
HUNT, J. R. (1914), *Amer. J. med. Sci.*, **147**, 704.
JAHNKE, E. J., and SEELEY, S. F. (1953), *Ann. Surg.*, **138**, 158.
JEPSON, R. P. (1955), *Brit. med. J.*, **2**, 405.
JOHNSON, J. K. (1954), *Arch. Surg., Chicago*, **69**, 663.
JULIAN, O. C., DYE, W. S., OLWIN, J. H., and JORDAN, P. H. (1952), *Ann. Surg.*, **136**, 459.
— — GROVE, W. J., DYE, W. S., JAVID, H., and SADOVE, M. S. (1954), *Ann. intern. Med.*, **41**, 36.
— — — — — — OLWIN, J., and SADOVE, M. S. (1953), *Ann. Surg.*, **138**, 387.
KEKWICK, A. (1951), *Proc. R. Soc. Med.*, **44**, 983.
KINMONTH, J. B., TAYLOR, G. W., and LEE, R. H. (1955), *Brit. med. J.*, **1**, 1406.
KOVANOV, V. (1955), Personal communication.
KUNLIN, J. (1949), *Arch. Mal. Cœur*, **42**, 371.
LAM, C. R., and ARAM, H. H. (1951), *Ann. Surg.*, **134**, 743.
LEARMONTH, J. R. (1940), *Edinb. med. J.*, **47**, 225.
— — BLACKWOOD, W., and RICHARDS, R. L. (1944), *Ibid.*, **51**, 1.
LERICHE, R. (1923), *Bull. Soc. Chir. Paris*, **49**, 1404.
— — (1940), *Pr. méd.*, **48**, 601.
— — and KUNLIN, J. (1947), *Lyon chir.*, **42**, 675.
LEVIN, I., and LARKIN, J. H. (1909), *Proc. Soc. exp. Biol., N.Y.*, **5**, 109.
LEXER, E. (1913), *Verh. dtsch. Ges. Chir.*, **42**, 112.
LINTON, R. R. (1954), *Ann. Surg.*, **140**, 309.
— — (1955 a), Personal communication.
— — (1955 b), *Surgery*, **38**, 817.
LUKE, J. C. (1954), *Arch. Surg., Chicago*, **69**, 205.
MAHORNER, H., and SPENCER, R. (1954), *Ann. Surg.*, **139**, 439.
MAKINS, G. W. (1919), *Gunshot Injuries to the Blood Vessels*. Bristol: Wright.
MARRANGONI, A. G., and CECCHINI, L. P. (1951), *Ann. Surg.*, **134**, 977.
MARTIN, P., and LYNN, R. B. (1952), *Brit. J. Surg.*, **59**, 352.
MERKER, I. A., and GROSS, R. A. (1951), *Science*, **114**, 283.
MILLIKAN, C. H., and SIEKERT, R. G. (1955), *Proc. Mayo Clin.*, **30**, 186.
MONIZ, E. (1927), *Rev. neurol.*, **2**, 72.
MOORE, H. G., NYHUS, L. M., KANAR, E. A., and HARKINS, H. N. (1954), *Surg. Gynec. Obstet.*, **98**, 129.
— — and TELLING, M. (1955), *Brit. J. Surg.*, **174**, 420.
MURPHY, J. B. (1897), *Med. Rec., N.Y.*, **51**, 73.
OLWIN, J. H., DYE, W. S., and JULIAN, O. C. (1953), *Arch. Surg., Chicago*, **66**, 480.
— — and FRIEDMAN, I. A. (1954), *Surg. Gynec. Obstet.*, **99**, 22.
OUDOT, J. (1951), *Mém. Acad. Chir.*, **77**, 642.
OWEN, K. (1955). Paper read at the Royal Society of Medicine, Dec.
PONTIUS, R. G., BROCKMAN, H. L., HARDY, E. G., COOLEY, D. A., and DEBAKEY, M. E. (1954), *Surgery*, **36**, 33.
POTTS, W. J., ALBURG, H., and FISCHER, H. W. (1953), *Ibid.*, **33**, 518.
PRINGLE, H. (1913), *Lancet*, **1**, 1795.
REBOUL, H., and LAUBRY, P. (1950), *Proc. R. Soc. Med.*, **43**, 547.
ROB, C. G. (1953), *Ibid.*, **46**, 121.
— — (1954 a), *Lancet*, **2**, 255.
— — (1954 b), *Proc. R. Soc. Med.*, **47**, 368.
— — (1954 c), *Ann. R. Coll. Surg., Engl.*, **14**, 35.
— — (1955 a), *Brit. med. J.*, **1**, 407.
— — (1955 b), *Ann. R. Coll. Surg., Engl.*, **17**, 307.
— — and EASTCOTT, H. H. G. (1953), *Brit. Surg. Pract.* (Progress Vol.), p. 1. London: Butterworth.
— — — — (1954 a), *Brit. J. Surg.*, **42**, 68.
— — — — (1954 b), *Lancet*, **1**, 573.
— — — — (1955 a), *Brit. med. J.*, **1**, 378.
— — — — (1955 b), *Brit. med. Bull.*, **11**, 217.
— — and HENSON, G. F. (1956), *Brit. J. Surg.* Accepted for publication in May issue.
SANDBLOM, P., MUREN, A., NORDEN, G., IDBOHIN, E., SANDEGARD, E., and DAHLBACK, O. (1953), *Acta chir. scand.*, **106**, 309.
SAUVAGE, L. R., and HARKINS, H. N. (1954), *West J. Surg.*, **62**, 7.
SCHAFER, P. W., and HARDIN, C. A. (1952), *Surgery*, **31**, 186.
SEELEY, S. F., HUGHES, C. W., and JAHNKE, E. J. (1952), *Amer. Coll. Surg., Surg. Forum*, 152.
SHAW, R. S., and WHEELOCK, F. (1955), *Surgery*, **37**, 94.
SHUMACKER, H. B., and KING, H. (1954), *Surg. Gynec. Obstet.*, **99**, 287.
SHUMWAY, N. E., GLIEDMAN, M. L., and LEWIS, F. J. (1955), *Ibid.*, **100**, 703.
SPENCER, F. C., and GREWE, R. V. (1955), *Ann. Surg.*, **141**, 304.
STRONG, W. R. (1954), *Ciba Foundation Symposium on the Preservation and Transplantation of Normal Tissues*, 220. London: Churchill.
SWAN, H., MAASKE, M., JOHNSON, R., and GROVER, C. (1950), *Arch. Surg., Chicago*, **61**, 732.
— — ZEAVIN, I., BLOUNT, G. G., and VIRTUE, R. W. (1953), *J. Amer. med. Ass.*, **153**, 1081.
SZILAGYI, D. E., and OVERHULSE, P. R., (1955), *Ibid.*, **157**, 426.
— — — — and LO GRIPPO, G. A. (1954), *Clin. Res. Proc.*, **2**, 108.
TRAFAS, P. C., CARLSON, R. W., LO GRIPPO, G. A., and LAM, C. R. (1954), *Arch. Surg., Chicago*, **69**, 415.
VOORHEES, A. B., JARETZKI, A. H., and BLAKEMORE, A. H. (1952), *Ann. Surg.*, **135**, 332.
WARREN, R., LINTON, R. R., and SCANNELL, J. G. (1954), *Ibid.*, **140**, 311.
WEGLOWSKI, R. (1925), *Zbl. Chir.*, **52**, 2241.
WYLIE, E. J. (1952), *Surgery*, **32**, 275.
— — and GARDENER, R. (1955), *Ibid.*, **37**, 415.

MICRO-ELECTROPHORETIC STUDIES OF PLASMA PROTEINS IN POST-OPERATIVE PATIENTS

By DOREEN A. BIRCH* and R. P. JEPSON†

FROM THE UNIVERSITY DEPARTMENT OF SURGERY, MANCHESTER ROYAL INFIRMARY

It has long been known that protein metabolism is markedly affected by trauma and by operations. The role which proteins play in the metabolic response to injury has been assessed in the past chiefly by studying nitrogen intake and loss and serum-protein levels. Many writers have emphasized the extent and duration of the negative nitrogen balance which occurs in post-operative patients (Cuthbertson, 1932; Brunschwig, Clark, and Corbin, 1942; Browne, Schenker, and Stevenson, 1944; Beattie, 1947; Wilkinson, Billing, Nagy, and Stewart, 1950; Pollack and Halpen, 1951; Moore and Ball, 1952; Rhoads, 1952; Cornell and Gilder, 1954), while studies on serum-protein levels, if not as extensive (Carsten, Bodenheimer, and Barcham, 1943; Ariel, 1949; Ravdin and Gimbel, 1950; Ariel, 1951), are perhaps less conclusive. Most authors have reported a fall in serum-protein level, although Elman (1944) has suggested that this index of protein metabolism in the post-operative patient is unreliable as many patients with a hypo-albuminæmia show a normal value for total proteins because of an increase in the globulin fraction due to infection. Again, if dehydration is present it may be responsible for a normal concentration of both fractions although the total amount of circulating protein is depleted.

It was thought that filter-paper electrophoresis might prove to be a suitable method to analyse the relative changes which occur in various fractions of plasma proteins in the first ten days after operation; a group of normal volunteers and patients undergoing operation were therefore investigated by this technique.

METHODS

Patients and Controls.—Fifteen patients and 8 normal controls selected for this study were grouped as follows:—

Group A.—Intra-abdominal surgery: partial gastrectomy (8 males), gastro-enterostomy (2 females, 1 male), laparotomy and mesenteric gland biopsy (1 male).

Group B.—Extra-abdominal surgery: biopsy of breast lump followed by radical mastectomy (1 female), inguinal herniorrhaphy (1 male), excision of anal papilloma (1 male).

Group C.—The control group which consisted of 8 healthy volunteers (3 females and 5 males).

The post-operative course of Groups A and B, with the exception of those cases mentioned in the text, was uneventful and none of the cases developed any surgical complication or abnormal fever.

Blood-sampling.—Arrangements were made to take fasting blood-samples whenever possible and the patients were confined to bed for at least one hour prior to venepuncture. Another precaution adopted throughout was to apply a pneumatic tourniquet to the upper arm immediately before venepuncture and to adjust the pressure to just below the diastolic blood-pressure level.

Micro-electrophoresis of Plasma Proteins on Filter-paper.—A modification of the method of Flynn and de Mayo (1951) was employed. The samples of plasma were from venous blood rendered incoaguable by the addition of 1 mg. of heparin per 10 ml. of blood.

A vertical electrophoresis tank mounted on a 250 volt power pack was used, and the optical density of the filter-paper strips was measured in a scanner fitted with a green glass filter.

The buffer solution used to fill the four compartments of the electrophoresis tank consisted of soluble barbitone (20 g.), sodium acetate (13·4 g.), *N* hydrochloric acid (14 ml.), and distilled water (up to 2 l.). The *p*H of alternate batches of this solution was tested on a moving coil *p*H meter and was found to vary between 8·6 and 8·8. Bromophenol blue (0·5 per cent in a saturated methanol solution of mercuric chloride) was employed for dyeing the paper strips which were subsequently washed in a solution of glacial acetic acid (1 per cent in distilled water), tap water, and technical ether. We found liquid paraffin unsuitable as a clarifier and therefore used a solution of tricresyl phosphate (50 parts) in light petroleum, b.p. 60°–80° C. (49 parts), and acetone (1 part) which proved highly satisfactory.

Electrophoretic Analysis of Fibrinogen Standards.—The following method was devised to establish the position of the fibrinogen peak in the electrophoretic fractionation of plasma proteins and to determine the percentage concentration of fibrinogen in the plasma which would manifest as a separate peak in electrophoretic analysis: 20 ml. of blood were withdrawn from a healthy adult male volunteer and allowed to clot. After centrifuging at 3000 r.p.m. for five minutes the serum was taken off and labelled Solution A. Solution B was made by adding 1 ml. of Solution A to an ampoule of dried sterile fibrinogen (1 ml. of 1·45 per cent fibrinogen). Solutions C, D, E, and F were made with double dilutions of 0·5 ml. of Solution A (*Table I*). 0·02 ml. of Solutions A–F were used for electrophoretic analysis, the results of which are represented in *Fig.* 561 and in the illustrated profiles obtained from

Table I.

Solution	A	B	C	D	E	F
Mg. fibrinogen per ml.	0	14·5	7·25	3·63	1·82	0·91

* Holding a Benger Research Fellowship; now at the Postgraduate Medical School of London.

† Now Professor of Surgery, University of Sheffield.

the filter-paper strips by an analysis of their optical density (*Fig.* 562).

The procedure was repeated with 2 other samples of different concentrations of fibrinogen and it was concluded that the fibrinogen remained stationary at the apex of the filter-paper and produced a peak proportional to the concentration of the protein. The averages of the values obtained in this way for each day are illustrated in *Fig.* 563. The figure −1 is used to denote the day preceding operation, 0 the day of operation and +1, +2, +3, etc., the days after operation. The follow-up study in Group A

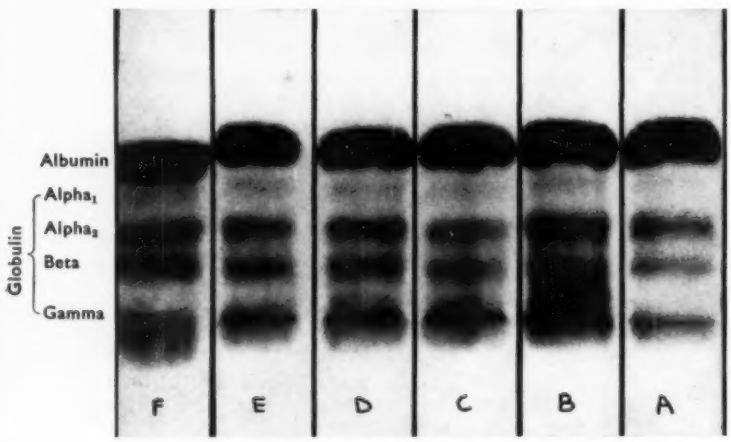


FIG. 561.—Filter-paper strips A–F. The dark strip in B–F gamma patterns represents the varying concentrations of fibrinogen.

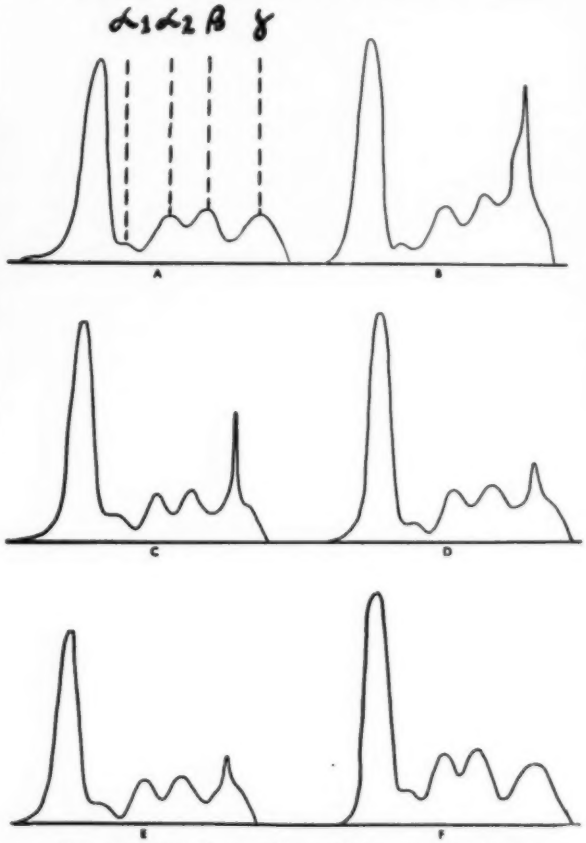


FIG. 562.—Peaks of alpha$_1$, alpha$_2$, beta, and gamma globulin are designated. The large initial peak is albumin fraction. The additional peak in B–E represents fibrinogen.

intermediate in position between the beta and gamma globulin fractions and that using this method of paper electrophoresis a fibrinogen peak was only apparent in the profile in concentrations at or above 2·5 mg. per ml. The height of this peak was augmented with increased concentrations of fibrinogen, but the height and area of the fibrinogen peak was not directly proportional to the amount of fibrinogen added.

RESULTS

It has been adequately proved that quantitative estimates of the plasma-protein fractions separated by electrophoresis are unreliable. Crook, Harris, Hassan, and Warren (1954) showed that the light absorption of dyed proteins in an immersed filter-paper did not obey Beer's law. Franglen and Martin (1954) in addition showed that the characteristics of the relation of dye-binding to protein concentration differ from one protein to another, and that if two protein solutions of known concentration are mixed in predetermined proportions and are then separated by electrophoresis, the proportions of these two components calculated by dye-binding techniques fail to tally with the predetermined ratio. In view of these difficulties no attempt was made to measure results quantitatively but instead the method of analysis employed in 8 cases in Group A and in the 3 cases in Group B was as follows :—

The area of the total globulin and fibrinogen fraction of the profile was measured with a compensating planimeter and in each sample this area was given the value of 100 per cent ; the area of each component of this part of the profile was measured and the result was expressed in terms of 100 per cent. The albumin peak was not included in these measurements because it seemed reasonable to presume that this fraction would be the most affected by the fact that the dye bound to it would not be was carried out approximately two months after discharge from hospital. The averages of the values of the different components in the control group are shown in *Table II.*

In Group C the plasma-protein profile studied for five consecutive days in each of the eight volunteers showed no apparent variations, an observation confirmed by the work of Dole (1944). At no time was a fibrinogen peak manifested.

Table II.

PROTEIN FRACTION	AVERAGE VALUE EXPRESSED AS A PERCENTAGE OF THE TOTAL GLOBULIN IN 8 NORMAL VOLUNTEERS (GROUP C)
Alpha$_1$ globulin	9·9
Alpha$_2$ globulin	23·9
Beta globulin	31·6
Gamma globulin	36·3
Fibrinogen	0

Fig. 564 is an illustrative example of one of the cases from Group A. This patient, a male aged 52 years, underwent a partial gastrectomy for a duodenal

ulcer and an anastomotic ulcer which had developed at the site of a gastro-enterostomy done thirteen years previously. An example of one of the cases in Group B is given in *Figs.* 565, 566. This patient, a female aged 49 years, was admitted for removal of a lump in the breast which had been diagnosed pre-operative values and remain level until the tenth day. (We only followed 3 cases in Group A to the fifteenth day and therefore the results were not included in *Fig.* 563 but all of these showed a very striking increase in gamma globulin again at or about the fifteenth day.)

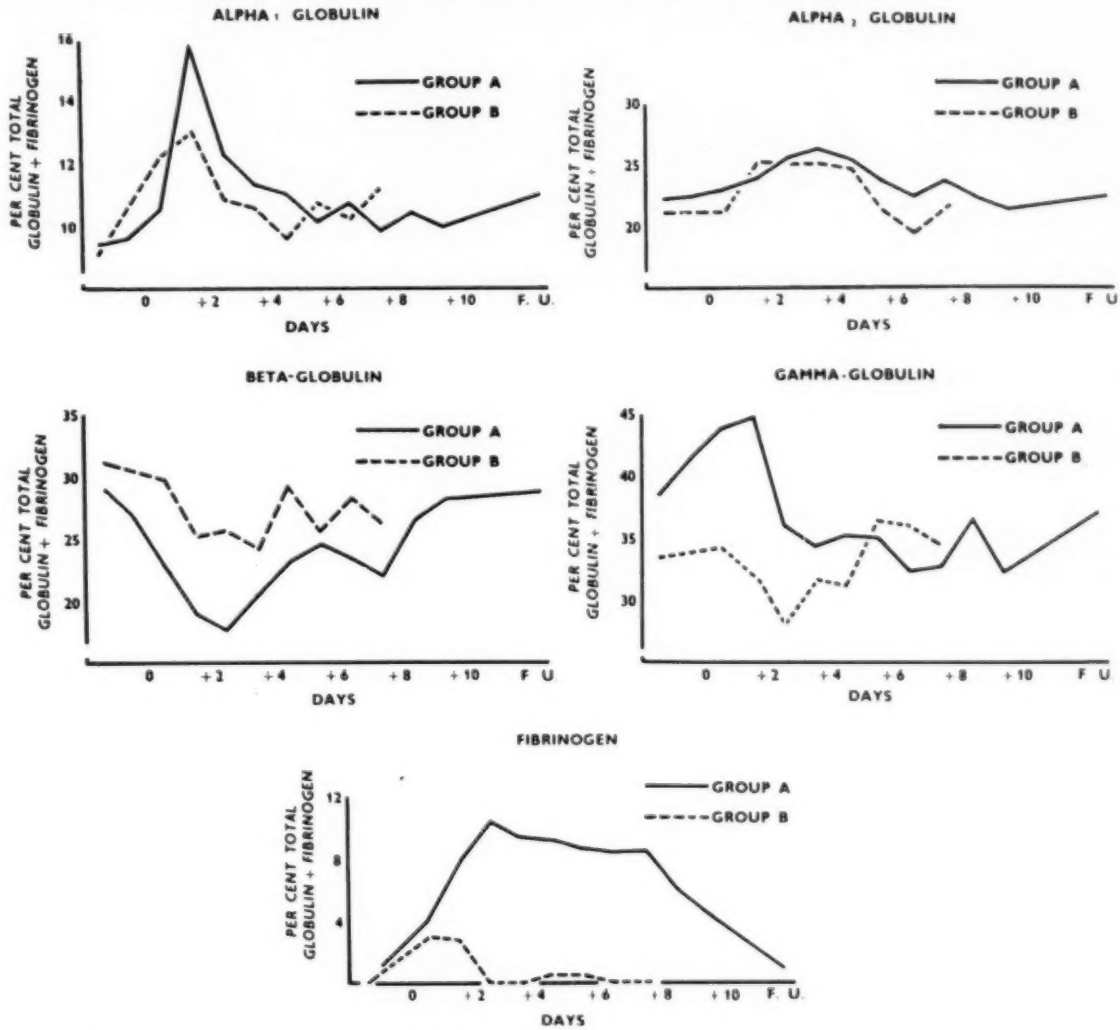


FIG. 563.—Plasma-protein changes after operation. Group A. Intra-abdominal surgical procedures. Group B. Extra-abdominal surgical procedures.

as chronic mastitis. The histological report, however, showed her to have had a sarcomatous transformation in an area of cystic mastopathy and she therefore underwent a radical mastectomy one week after the first operation.

It was interesting to note that the only cases which showed the presence of a fibrinogen peak before operation were two of three patients in Group A admitted with carcinoma of the stomach.

From the analysis of our results we are able to conclude that the usual response to intra-abdominal surgical procedures in patients (Group A) in order of development is :—

1. A rise in alpha$_1$ globulin which reaches a maximum on the second post-operative day, accompanied by a similar rise in gamma globulin ; thereafter both these fractions tend to return to the

2. A fall in beta globulin which is maximal on the third and fourth days.

3. A rise in alpha$_2$ globulin maintained from the second to the sixth days.

4. A rise in plasma fibrinogen which is maintained at a maximal level from the third to the eighth day after operation and thereafter returns to the pre-operative levels. The follow-up studies were similar to the pre-operative ones. No difference was noted between males and females or in the different age groups.

The response in Group B differs from that in Group A in that it is less marked (particularly with regard to the fibrinogen fraction), although of a similar pattern.

Three cases were not included in *Fig.* 563 because two of these showed abnormal peaks in

the post-operative period. One case was male, aged 36 years, who underwent a partial gastrectomy for a duodenal ulcer. On the second post-operative day he became gravely ill and his condition was diagnosed clinically as being due to a duodenal stump leak. He was treated conservatively with intravenous saline and glucose and improved response. It became apparent again, however, on the sixth day. The follow-up study showed a marked increase in beta globulin, but the form of the gamma-globulin fraction was hidden by the fibrinogen. The third case, not included in *Fig.* 563, a female aged 62 years, was admitted with pyloric stenosis due to a benign cicatrizing pyloric

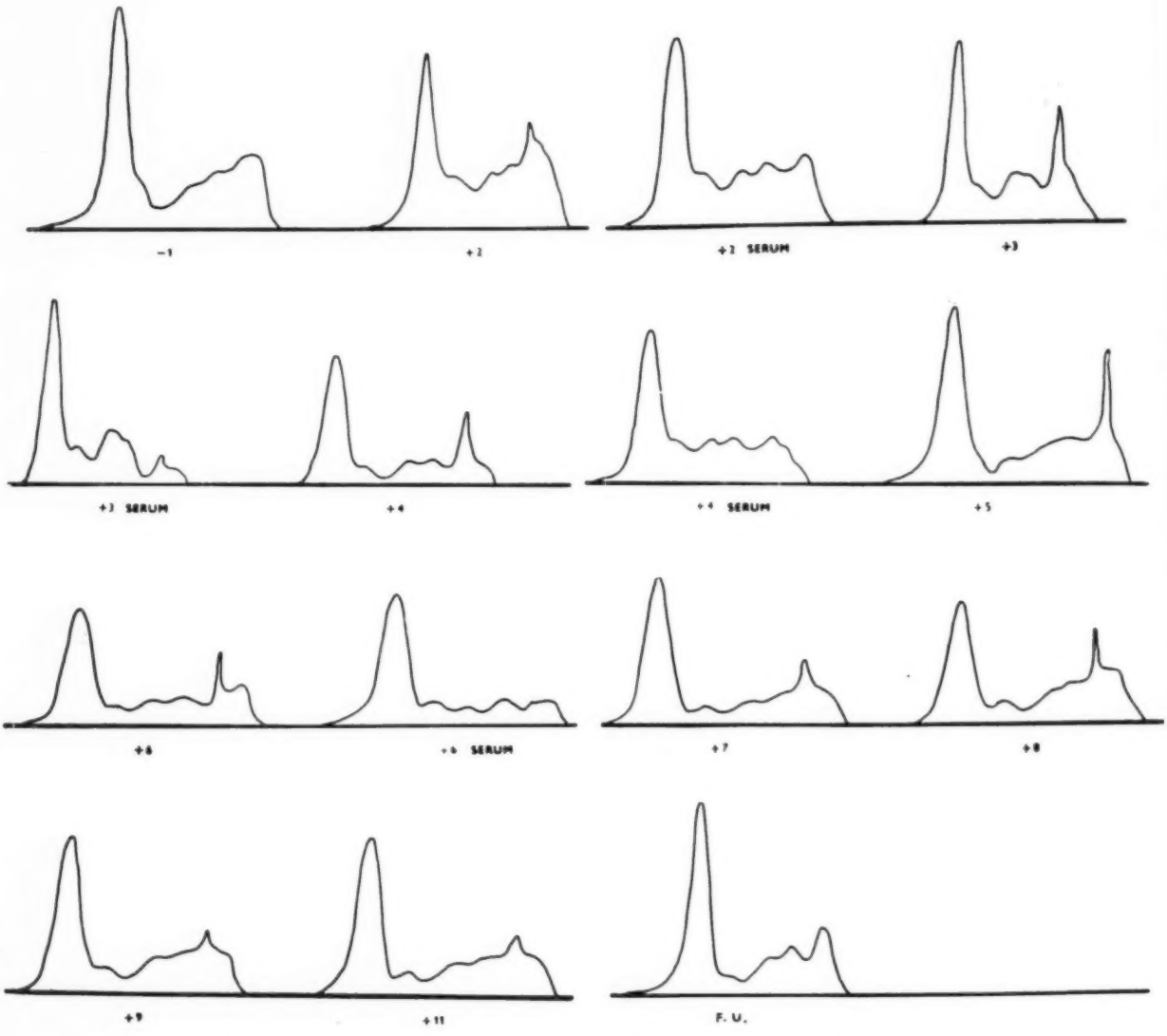


FIG. 564.—Plasma-protein profiles of a male aged 52 years (partial gastrectomy).

steadily. On the fourth day, however, his profile showed an extra peak intermediate to the beta and gamma globulin in the position of $beta_2$ globulin. This disappeared after the fifth day. In other respects his reaction was the same as shown in *Fig.* 563 for the patients in Group A. The other case with an abnormal profile was a male, aged 41 years, found at operation to have an inoperable carcinoma of the stomach with multiple metastases in the liver. A mesenteric gland was removed for biopsy but no other procedures were carried out. Before operation he showed a bifid gamma-globulin peak which was occluded on the third day by a marked fibrinogen ulcer. On the fourth post-operative day the profile showed a marked elevation of the $alpha_2$ globulin and fibrinogen peaks. These two components continued to increase in size until the ninth day when she complained of precordial pain and became severely shocked. An electrocardiograph taken at that time showed evidence of posterolateral myocardial ischæmia. *Fig.* 567 illustrates the pre-operative profile in this case, and the post-operative profiles on the seventh and eighth days which show the great increase in $alpha_2$ globulin and fibrinogen prior to the clinical onset of coronary thrombosis.

DISCUSSION

From the analysis of electrophoretic changes in plasma proteins it is apparent that a definite pattern is produced in response to surgical operations.

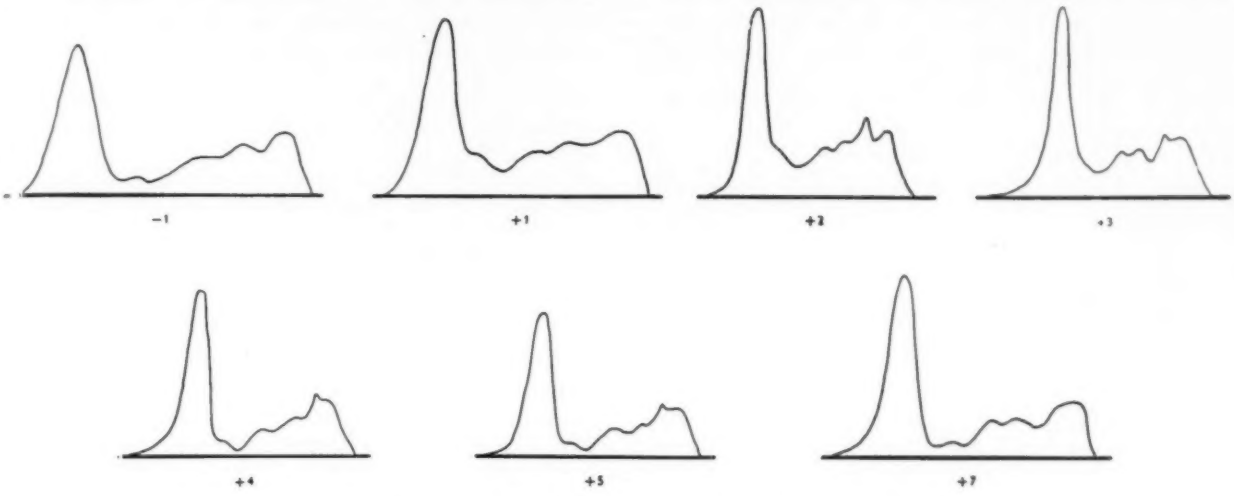


FIG. 565.—Plasma-protein profiles of a female aged 49 years (local excision of a lump in the breast).

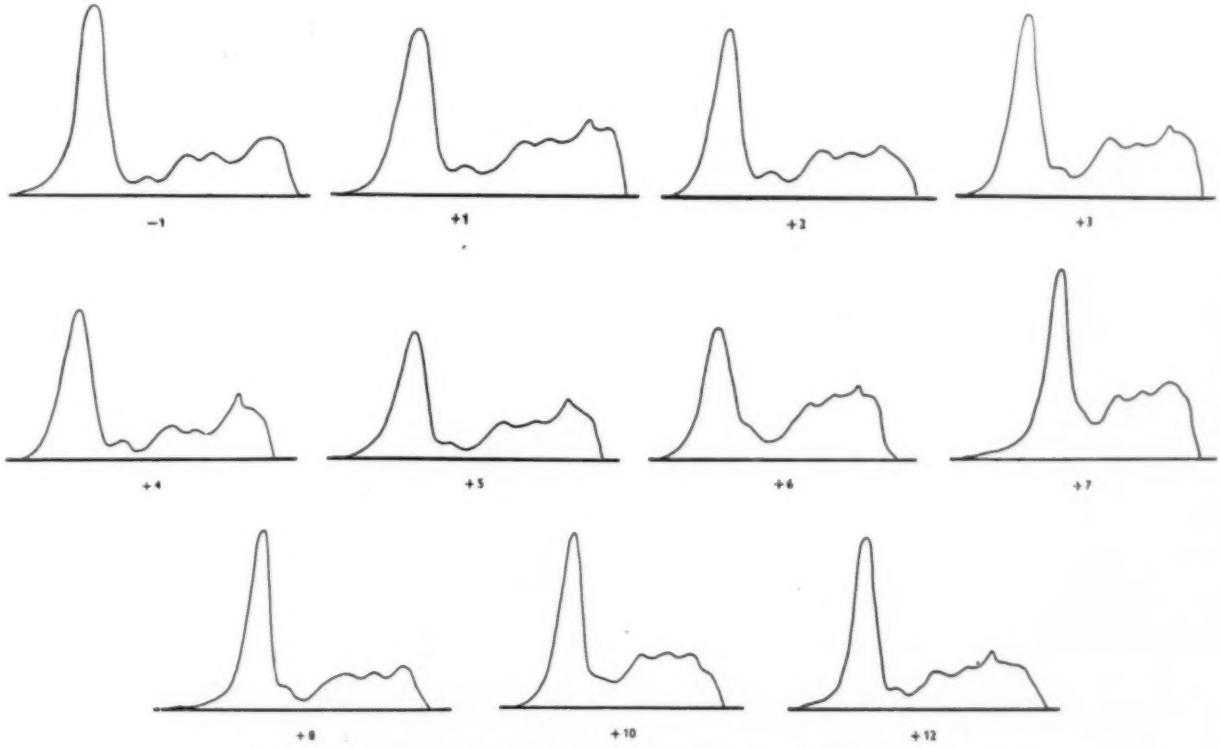


FIG. 566.—Plasma-protein profiles of a female aged 49 years (radical mastectomy).

This is confirmed by the work of Margulis, Wiseman, Moyer, and Pratt (1952) and Hogh-Ligeti, Irvine, and Sprinkle (1953) who used a similar technique. Moreover, Chanutin and Gjessing (1946), who analysed the sera of injured dogs by electrophoresis, reported a decrease in albumin concentration and an increase in the alpha-globulin fractions; and Perlman, Glenn, and Kaufman (1943) obtained similar results in experimental work on calves exposed to severe burns.

Electrophoretic analyses of plasma and serum have been reported in a great variety of diseases and the reader is referred to two reviews of the subject (Luetscher, 1947; Marrack and Hoch, 1949). From a study of the literature it would appear that a response similar to the one which we have encountered in post-operative patients is also found in severe systemic infections (Luetscher, 1941; Dole, Watson, and Rothbard, 1945; Cohn and Lidman, 1946; Malmros and Blix, 1946; and

Flynn, 1954), but the interpretation of this phenomenon is open to speculation.

We would draw attention to the fact that the response to surgery measured by plasma-protein electrophoretic fractionation may be modified by the site of the operation, in addition to the extent of the trauma. (*Figs.* 565, 566.) The response to the first minor operation (the removal of the lump in the breast (*Fig.* 565)) is almost identical to

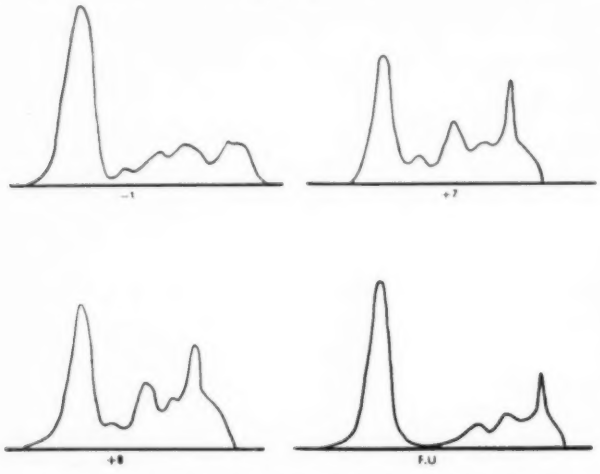


FIG. 567.—Plasma-protein profiles of a female aged 62 years (partial gastrectomy) coronary thrombosis on the 9th post-operative day.

the response after the second major operation (radical mastectomy (*Fig.* 566)), although after both operations the changes were never as marked as in any of the cases undergoing intra-abdominal surgical procedures. It is well recognized that the metabolic response to a second operation within two to three weeks of a first is much less marked and this may hold for the electrophoresis pattern.

It is interesting to note that the fibrinogen response to surgery apparent in electrophoretic studies is consistent with the results of other workers who measured this plasma-protein fraction quantitatively (Foster and Whipple, 1921; Gughelmeffi, Babolini, and Valerio, 1939; Cummine and Lyons, 1948; Payling Wright, 1948; Henriques, Henriques, and Mattos, 1950; Warren, Amdur, Belko, and Baker, 1950). Whether the increase in plasma fibrinogen can be related to intravascular thrombosis after operation is difficult to decide. We were, however, impressed with the striking pattern changes in *Fig.* 567. The question that arises here is whether or not the changes were due to the developing coronary artery occlusion, or whether the precipitating factor in the onset of coronary thrombosis was something entirely different which itself produced the grossly exaggerated protein response. Further investigation in patients likely to develop thrombosis or cardiac disease after operation would perhaps answer this problem and electrophoretic protein estimations might then be valuable in providing an indication for prophylactic therapy.

Finally, it is not possible at this stage to suggest the reasons underlying the electrophoretic response to surgery. Various authors (Cohn, Oncley, Strong, Hughes, and Armstrong, 1944; and Martin, 1949) have suggested that the different components of the globulin fractions are concerned with a variety of physiological functions, e.g., the alpha globulins carry bilirubin and hypertensinogen, and they are associated with lipids insoluble in water; beta globulin carries vitamin A, steroid hormones, hypertensinogen, thrombin, isohæmagglutinin, and some complement C^1, and like the alpha globulins it is associated with lipoproteins; gamma globulin carries antibodies, isohæmagglutinin, and complement C^1. Therefore it must be borne in mind that when measured by electrophoresis an increase or decrease in any of these plasma-protein fractions may be associated with the factors combined with them. This opens up another field of research in the complex problem of metabolic studies in surgery.

SUMMARY

1. Plasma-protein changes measured by micro-electrophoresis are described in 15 patients who underwent various surgical procedures and in 8 healthy volunteers who served as a control group.

2. Results indicated a definite pattern response to surgery which, however, was most marked in patients who underwent major intra-abdominal surgical procedures.

3. References have been made to the work of others in the literature and various suggestions have been advanced about the possible significance of the changes in plasma-protein behaviour after operation, although it has been pointed out that no conclusions are possible until more research has been done.

We gratefully acknowledge the facilities provided by Professor A. M. Boyd, Professor of Surgery, University of Manchester. We would also like to thank Dr. H. G. B. Slack, Department of Rheumatism Research, University of Manchester, for helpful advice and suggestions. The illustrations in this paper were prepared for publication by the Department of Medical Illustration, Manchester Royal Infirmary.

ADDENDUM

Since this paper was written, work by Mr. M. W. Reece in the University Department of Surgery, Sheffield, with fibrinogen estimations has convinced us that this paper method has no advantages over the chemical technique.

REFERENCES

ARIEL, I. M. (1949), *Surg. Gynec. Obstet.*, **88**, 185.
— — (1951), *Ibid.*, **92**, 404.
BEATTIE, J. (1947), *Brit. med. J.*, **1**, 813.
BROWNE, J. S. L., SCHENKER, V., and STEVENSON, J. A. F. (1944), *J. clin. Invest.*, **23**, 932.
BRUNSCHWIG, A., CLARK, D. E., and CORBIN, N. (1942), *Ann. Surg.*, **115**, 1091.
CARSTEN, D., BODENHEIMER, M., and BARCHAM, I. (1943), *Ibid.*, **117**, 52.
CHANUTIN, A., and GJESSING, E. C. (1946), *J. biol. Chem.*, **165**, 421.
COHN, C., and LIDMAN, B. I. (1946), *J. clin. Invest.*, **25**, 145.
COHN, E. J., ONCLEY, J. L., STRONG, L. E., HUGHES, W. L., and ARMSTRONG, S. H. (1944), *Ibid.*, **23**, 417.

CORNELL, G. N., and GILDER, H. (1954), *Surgery*, **36**, 468.
CROOK, E. M., HARRIS, H., HASSAN, F., and WARREN, F. L. (1954), *Biochem. J.*, **56**, 435.
CUMMINE, H., and LYONS, R. N. (1948), *Brit. J. Surg.*, **35**, 337.
CUTHBERTSON, D. P. (1932), *Quart. J. Med.*, **25**, 233.
DOLE, V. P. (1944), *J. clin. Invest.*, **23**, 708.
— — WATSON, R. F., and ROTHBARD, S. (1945), *Ibid.*, **24**, 648.
ELMAN, R. (1944), *Ann. Surg.*, **120**, 350.
FLYNN, F. V. (1954), *Proc. R. Soc. Med.*, **47**, 827.
— — and DE MAYO, P. (1951), *Lancet*, **2**, 235.
FOSTER, D. P., and WHIPPLE, G. H. (1921), *Amer. J. Physiol.*, **58**, 407.
FRANGLEN, G. T., and MARTIN, N. H. (1954), *Biochem. J.*, **57**, 626.
GUGHELMEFFI, P., BABOLINI, G., and VALERIO, M. (1939), *Arch. ital. Chir.*, **55**, 185.
HENRIQUES, S. B., HENRIQUES, O. B., and MATTOS, L. (1950), *Endocrinology*, **47**, 457.
HOGH-LIGETI, C., IRVINE, K., and SPRINKLE, E. P. (1953), *Proc. Soc. exp. Biol., N.Y.*, **84**, 707.
LEUTSCHER, J. A. (1941), *J. clin. Invest.*, **20**, 99.
— — (1947), *Physiol. Rev.*, **27**, 621.
MALMROS, H., and BLIX, G. (1946), *Acta med. scand.*, Suppl. 170, p. 280.
MARGULIS, R. R., WISEMAN, M. E., MOYER, E. Z., and PRATT, J. P. (1952), *Surgical Forum*, 571. London: W. B. Saunders Co.
MARRACK, J. R., and HOCH, H. (1949), *J. clin. Path.*, **2**, 161.
MARTIN, N. H. (1949), *J. Amer. chem. Soc.*, **71**, 1230.
MOORE, F. D., and BALL, M. R. (1952), *The Metabolic Response to Surgery*. Springfield, Ill.: Charles C. Thomas.
PERLMAN, G. E., GLENN, W. W. L., and KAUFMAN, D. (1943), *J. clin. Invest.*, **22**, 627.
POLLACK, H., and HALPEN, S. L. (1951), *Advanc. Protein Chem.*, **6**, 383.
RAVDIN, I. S., and GIMBEL, N. S. (1950), *J. Amer. med. Ass.*, **144**, 979.
RHOADS, J. E. (1952), *Int. Abstr. Surg.*, **94**, 417.
WARREN, R., AMDUR, M. O., BELKO, J., and BAKER, D. U., jun., (1950), *Arch. Surg., Chicago*, **61**, 419.
WILKINSON, A. W., BILLING, B. H., NAGY, G., and STEWART, C. P. (1950), *Lancet*, **1**, 533.
WRIGHT, H. PAYLING (1948), *Proc. R. Soc. Med.*, **41**, 17.

VARIATIONS IN THE BLOOD-SUPPLY OF THE UPPER JEJUNUM

BY T. E. BARLOW

DEPARTMENT OF ANATOMY, MEDICAL SCHOOL, KING'S COLLEGE, UNIVERSITY OF DURHAM, NEWCASTLE UPON TYNE

THERE appears to be an increasing tendency in modern surgical practice to utilize portions of the upper coils of jejunum to replace sections of the alimentary canal affected by certain pathological lesions. For some years operations have been carried out to replace the œsophagus in this way and jejunum has also been used to replace the stomach.

Some surgical procedures necessitate division of jejunal arteries near their origins from the superior mesenteric in order to allow mobilization of the required portion of jejunum. Robertson and Sarjeant (1950) say that it may be necessary to divide the first four or five jejunal branches, leaving the intestine in that region dependent upon retrograde flow through the arterial arcades. Allison and da Silva (1953) point out that there may be certain dangers in dividing these vessels as the arrangement of vascular arcades in the mesentery is subject to variation, and that in occasional patients the arrangement of the arteries is so unusual and unusable that a long Roux loop cannot be made.

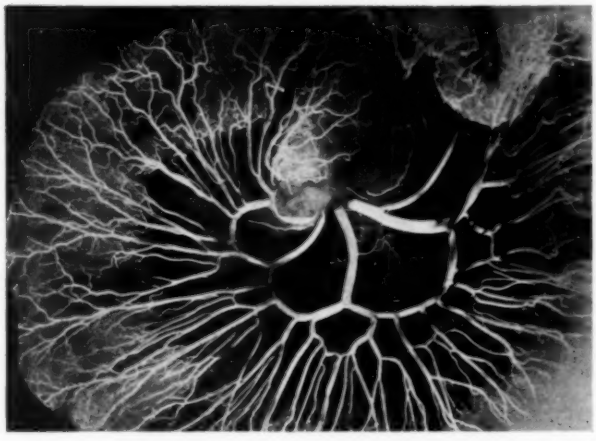


FIG. 568.—Radiograph of a normal arcade pattern. Vessels outlined with 20 per cent chlorbismol. (× 0·5.)

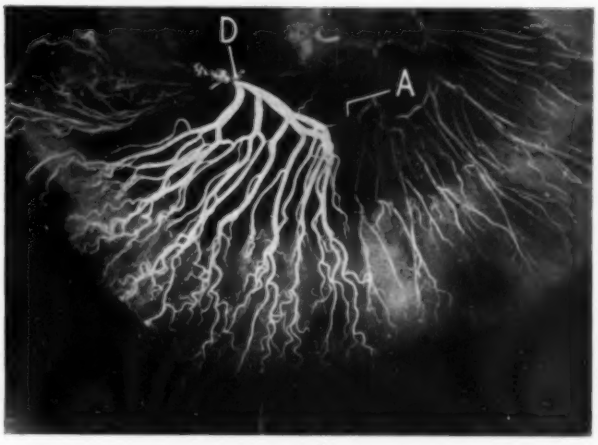


FIG. 569.—Radiograph of an abnormal arcade pattern. Vessels outlined with 20 per cent chlorbismol. D, Duodenal end of arcade. A, Narrow link in the arcade system. (× 0·75.)

With these observations in mind an investigation of the arterial arcades of the upper loops of jejunum has been made and the common variations noted. Portions of jejunum supplied by the upper 5 or 6 jejunal arteries were obtained from the post-mortem room. The jejunal arteries supplying the loop were ligated close to the superior mesenteric artery and

in each case a cannula was introduced into the arterial arcade either at the duodenal or at the distal end. Injections of 20 per cent chlorbismol were made into the arcade in each specimen at normal blood-pressure levels and radiographs were produced to demonstrate the outline of the vascular pattern.

The second was an arcade in which one of the linking vessels was extremely small with an internal diameter as measured on the radiographs of less than 0·5 mm. (*Fig.* 569). In this particular specimen the injection did not outline the arcade beyond the narrow vessel till pressure had been raised by an additional 80 mm. to 200 mm. Hg, and even then the amount that flowed across was only enough to outline the remaining vessels faintly.

FIG. 570.—Photograph of a specimen with abnormal arcade. Rods are inserted into the cut ends of three jejunal arteries. Note the complete absence of any vessel in the mesentery between two adjacent jejunal vessels. (× 0·45.)

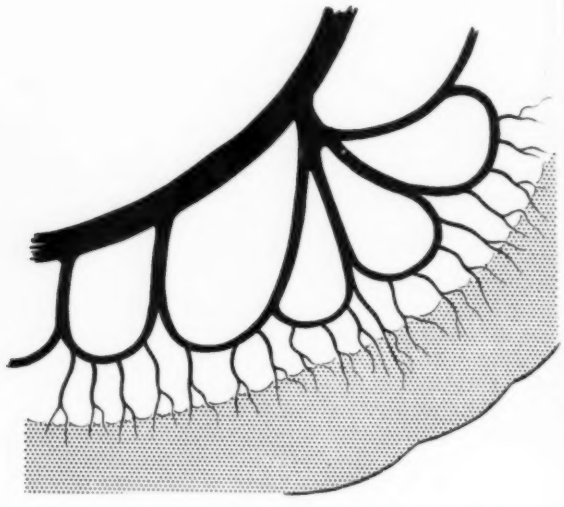


FIG. 571.—Diagram indicating the manner in which several jejunal vessels may arise from a common trunk.

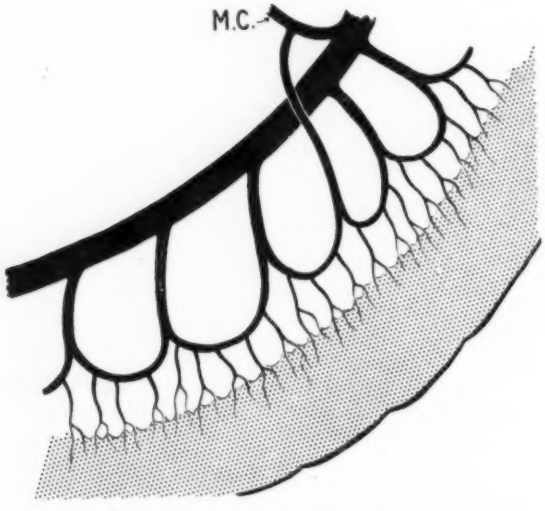


FIG. 572.—A jejunal vessel arising from the middle colic artery. M.C., Middle colic artery.

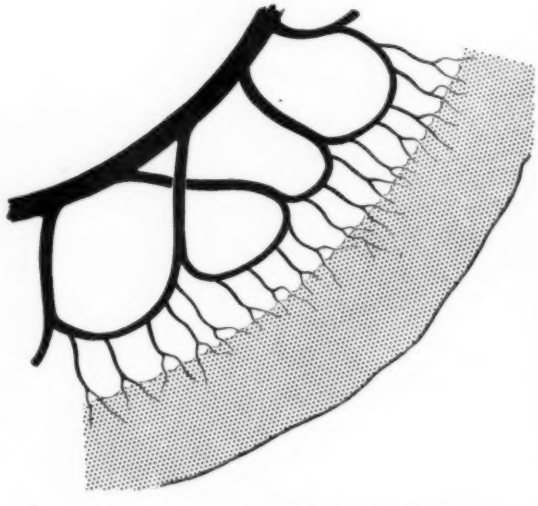


FIG. 573.—Jejunal arteries crossing over each other as they leave the superior mesenteric vessel.

Chlorbismol outlines all vessels except those of capillary size and a clear view is thus obtained of the arcade, the branches to the intestine, and the major intramural ramifications.

Examination of a small series in this manner demonstrated that three types of arcade might be present.

The first was the normal arcade pattern commonly described in current text-books of anatomy, the lateral linkages of which were made up of vessels of anything from 2–5 mm. in internal diameter as measured directly on the films (*Fig.* 568).

The third was an arcade with complete absence of one of the linkages—no vessels were seen in the mesentery linking two adjacent arteries (*Fig.* 570).

Observations made on dissecting room material throughout the country have enabled a large number of arcades to be examined. Thus it has been possible to determine the frequency of occurrence of these variations which might be of surgical significance.

In all a total of 257 arcades have been examined and of these 201 (78·6 per cent) were normal, 41 (15·7 per cent) showed weak linkages between adjacent jejunal arteries, and 15 (5·7 per cent) had an arcade in which one of the lateral linkages between adjacent jejunal arteries was missing.

Other variations were revealed during the course of the investigation. Out of a total of 123 diagrams sent in by various observers 17 (14 per cent) showed a superior mesenteric artery in which a common trunk gave rise to two or more jejunal branches (*Fig.* 571), and in one case all five upper jejunal branches were arising from a common trunk. Rarer variations which are probably of academic interest only are illustrated in *Figs.* 572, 573. The first of these (*Fig.* 572) demonstrates an arcade in which one of the jejunal branches originates from the middle colic artery, the second an arcade in which two of the jejunal arteries cross over each other as they leave the superior mesenteric vessel. These variations each occurred once throughout the series.

DISCUSSION

In the presence of a normal arcade (*Fig.* 568) the indications are that there is no hindrance to the rapid retrograde flow of blood via the arcade in such quantity as to maintain viability following the ligation of the vessels of direct supply.

When there is a weak link in the arcade system as in the first variation described (*Fig.* 569) the blood-supply of the proximal end must be precarious when the main jejunal branches are severed. The piece of intestine shown in *Fig.* 569 was injected from the duodenal end of the arcade at normal blood-pressures and the portion heavily outlined filled immediately. No injection flowed into the remainder of the specimen until the pressure was raised to 200 mm. Hg and then only enough material flowed to outline the vessels faintly. The narrow communication in the arcade system is shown, but it is possible that the distal arcade system has filled from intramural anastomoses in addition to the weak mesenteric link.

The marked obstruction to the flow of an injection mass does not necessarily mean that there would be such resistance under physiological conditions following ligation of jejunal vessels, but it does mean that where such narrow linkages are observed to exist the very greatest care must be exercised in preparing a jejunal loop for transplantation. A venous arcade of normal size is no guarantee that the arterial arcade is normal also and direct observation of the arterial arcade is always necessary. This variation was more commonly observed between the 2nd and 3rd, or 4th and 5th jejunal arteries.

The second variation (*Fig.* 570), observed most frequently between jejunal arteries 1 and 2, or 2 and 3, demonstrates a complete break in the arcade system which in this particular instance involved the venous arcade also. It is not possible to state whether this is always the case, but it is very probable that a venous arcade may be present when there is a complete break in the arterial linkage. If there were division of the jejunal branches from the superior mesenteric artery in such an instance, the blood-supply of the proximal portion would depend entirely upon intramural anastomoses in the jejunum. Although the presence of such intramural anastomoses is firmly denied by Cokkinis (1930) their presence has been amply demonstrated by Noer (1943), Eisberg (1924), Doran (1950), and Ross (1952), though their efficiency in maintaining a collateral circulation has been shown to be doubtful. The internal diameter of these intramural anastomoses is between 100μ and 140μ (Barlow, 1952) and a suitable injection material will flow freely through them over a period of minutes. It is quite certain, however, that they are not sufficiently large to maintain viability of a piece of jejunum divorced from its direct supply from the arterial arcade.

Evidence for this is to be found in the fact that according to Allison and da Silva (1953) division of too many jejunal arteries may cause inadequate circulation, through the most proximal portion of jejunum, even in the presence of a normal arcade. The experimental evidence of Eisberg (1924) who found in dogs that following ligation of the intestinal arteries the safety factor was nil, also lends support to the fact that the intramural anastomoses of intestinal vessels are totally inadequate to maintain viability following loss of direct blood-supply to the area.

SUMMARY

1. Approximately 1 in 5 of all jejunal arterial arcades show some variation, the commonest being a vessel of narrower diameter than usual between two adjacent jejunal arteries.

2. Approximately 1 in 20 of all jejunal arcades will have a complete interruption.

3. Other modes of origin of jejunal arteries are described in which the arcade system may be normal.

4. Unless the arcade system is completely normal difficulties may be encountered in maintaining the viability of the jejunum, should the necessity for mobilization of that organ occur.

It is a pleasure to acknowledge the contribution made by members of staff of anatomy departments in many medical schools, without whose help the amassing of the large number of observations would have been long and tedious. My thanks are also due to Mr. D. P. Hammersley who produced the diagrams and to Mr. F. S. A. Doran who made many helpful suggestions.

REFERENCES

ALLISON, P. R., and DA SILVA, L. TAVARES (1953), *Brit. J. Surg.*, **41**, 173.

BARLOW, T. E. (1952), *A Ciba Foundation Symposium*, 21. London: J. & A. Churchill.

COKKINIS, A. J., (1930), *J. Anat., Lond.*, **64**, 200.

DORAN, F. S. A. (1950), *Ibid.*, **84**, 283.

EISBERG, H. B. (1924), *Anat. Rec.*, **28**, 227.

NOER, R. J. (1943), *Amer. J. Anat.*, **73**, 293.

ROBERTSON, R., and SARJEANT, T. R. (1950), *J. thorac. Surg.*, **20**, 691.

ROSS, J. A. (1952), *Brit. J. Surg.*, **39**, 1.

THE SURGICAL TREATMENT OF FAMILIAL POLYPOSIS OF THE COLON

By H. E. LOCKHART-MUMMERY, CUTHBERT E. DUKES, AND H. J. R. BUSSEY

FROM ST. MARK'S HOSPITAL, CITY ROAD, LONDON

FAMILIAL intestinal polyposis is a hereditary disease characterized by the development in childhood or early adult life of great numbers of adenomatous tumours within the mucosa of the colon and rectum. It is a rare disease, but we can claim to have had exceptional opportunities for studying it because for the last thirty years a research into its origin and treatment has been pursued at St. Mark's Hospital. The hospital now has records of 58 families in which this disease has occurred and in each of these the affected members have been investigated, as many relatives as possible have been traced, and a family pedigree prepared. These 58 families now include 1069 members (using the word 'member' to describe polyposis patients, their brothers and sisters and direct descendants), amongst whom no less than 218 are known to have suffered from polyposis and 154 to have developed intestinal cancer.

This paper is concerned only with the problem of the surgical treatment to be adopted in familial intestinal polyposis. The clinical course and manner of inheritance have recently been described by one of us (Dukes, 1952) and the main facts may be summarized briefly as follows: Tumours first appear in affected members in childhood or early adult life, the average age of onset of symptoms being about 20 years. It is rare for symptoms to develop for the first time after the age of 40. Cancer is most likely to be discovered about fifteen years after the first onset of symptoms of polyposis, that is to say, on the average at about 35 years of age. Polyposis may affect males and females equally and either may transmit the disease, but in most polyposis families only half the children will inherit the abnormality, the remainder being normal. Affected members are likely to transmit polyposis to the next generation in accordance with the laws which govern the Mendelian inheritance of a dominant factor. The possibility of transmission by apparently unaffected members cannot yet be finally excluded, but in the meantime it can be said that unaffected members of a polyposis family are very unlikely indeed to transmit the disease. A similar large-scale investigation of a group of polyposis families recently undertaken by Gardner (1951) in America has led to very similar conclusions.

A clear picture of the possibilities and limitations of surgical treatment can only be obtained by a survey of a large series of cases, and so for the purpose of this paper we have reviewed all the familial polyposis patients treated at St. Mark's Hospital between the years 1918 and 1954. We are much indebted to all our colleagues, past and present, who have so generously allowed us to include all their cases and have often also assisted us by giving additional information. This has enabled us to collect a consecutive series of 60 cases of intestinal polyposis all of which were treated by major abdominal surgery. Two of these cases are illustrated on p. 480 (*Figs.* 575–578).

One of the objects of this paper is to show how greatly the results of surgical treatment of polyposis have improved during recent years and to emphasize this it will help if we divide these 60 cases into two groups. The first 21 were treated in the period 1918–45 and we shall refer to these as the first series. The remaining 39 cases have been treated since 1946: we shall describe these as the second series. We are making this distinction because in 1946 special efforts were made to trace relatives of previously treated cases, some of whom were visited in their homes and others invited by letter to attend for examination. Naturally this resulted in the discovery of cases at an early stage of the development of the disease so that the 39 cases treated during the last nine years are not strictly comparable with the 21 cases treated in the first twenty-seven years.

THE FIRST SERIES: 21 CASES TREATED FROM 1918 TO 1945 INCLUSIVE

The method of surgical treatment adopted for these early cases was as follows:—

14 were treated by excision of the rectum
4 by subtotal colectomy with anastomosis of ileum to rectum or sigmoid
3 by a partial resection of colon with Paul-Mikulicz anastomosis.

The results are summarized in *Table I* from which it will be seen that of the 14 patients treated by excision of the rectum 3 died from the operation, 4 from recurrence or other diseases, 3 developed new primary carcinomas of the colon, and 4 are still alive. Of the 4 treated by colectomy and anastomosis 2 died from the operation, 1 developed a new primary in the retained sigmoid colon, and 1 still survives. The 3 treated by resection are all deceased. One died from other causes one year after resection of the colon and the other two developed new primary carcinomas.

These, briefly stated, are the facts with regard to the first series of 21 cases, and two points arrest attention at once. The first is that the operative mortality in the years 1918–45 was disturbingly high, being 23 per cent. The second is that 6 of the original 16 operation survivors subsequently developed another primary tumour in the remaining bowel.

THE SECOND SERIES: 39 CASES TREATED FROM 1946 TO 1954 INCLUSIVE

The 39 patients in this second series were treated as follows:—

5 by total procto-colectomy with establishment of a permanent ileostomy
2 by a combined excision of the rectum and left hemicolectomy
1 by partial resection of the colon with anastomosis
2 by total procto-colectomy with ileo-anal anastomosis
29 by total colectomy with anastomosis of the ileum to the remaining rectal segment, the anastomosis being usually about 12 cm. from the anal verge.

In this second series one or more carcinomas were present in 14 of the 39 initial operation specimens, an incidence of malignant change of 35·9 per cent, whereas in the 21 cases of the first series cancer was found in the initial operation specimen in 11 cases, an incidence of 52·4 per cent. We think that the lower incidence of malignancy in the second series (35·9 per cent as compared with 52·4 per cent) is to be attributed to earlier treatment, being the direct consequence of the special effort made in tracing relatives of polyposis patients.

Table I.—CASES FROM 1918 TO 1945

METHOD	NUMBER	OPERATIVE DEATHS	DIED OF RECURRENCE OR OTHER DISEASE	DEVELOPED A NEW PRIMARY CARCINOMA	STILL LIVING
Excision of rectum	14	3	4	3	4
Colectomy and anastomosis	4	2	—	1	1
Resection	3	—	1	2	0
	21	5 (23 per cent)	5	6	5

The after history of the 39 patients in the second series is recorded in *Table II*, being set out in the same way as in *Table I*, but we must add some additional information about these later cases to explain why so many different surgical procedures were adopted.

Table II.—CASES FROM 1946 TO 1954

METHOD	NUMBER	OPERATIVE DEATHS	DIED OF RECURRENCE OR OTHER DISEASE	DEVELOPED A NEW PRIMARY CARCINOMA	STILL LIVING
Total procto-colectomy with ileostomy	5	1	1	—	3
Excision of rectum	2	—	2	—	0
Resection and anastomosis	1	—	1	—	0
Colectomy and ileo-anal anastomosis	2	—	—	—	2
Colectomy and ileo-rectal anastomosis	29	1 (3·4 per cent)	1	1	26
	39	2 (5·1 per cent)	5	1	31

Of the 5 patients treated by total procto-colectomy 4 were so treated because a carcinoma was already present in the rectum, and 1 because of such extensive polyposis that there was almost no normal rectal mucosa. One died as a result of the operation, and another has since died, probably of recurrent carcinoma, but we have been unable to determine the exact cause of death. Three of the 5 are still alive and remain well with no sign of recurrent disease.

The 2 patients treated by excision of the rectum and left hemicolectomy both had an advanced rectal cancer, and 1 also had secondary deposits in the liver and a second primary in the left colon. Both died of recurrence within two years, and the incomplete colectomy was done in the knowledge that any operation would only be palliative. The same consideration applied to the patient who was treated by resection of a colonic growth and anastomosis: he died of recurrence within a year.

Two patients were treated by removal of the entire colon and rectum with anastomosis of the ileum to the upper end of the anal canal. One of these was a woman with an advanced rectal carcinoma and the operation was done in the hope of sparing her an ileostomy. Unfortunately the anastomosis broke down and an ileostomy became necessary, but she remains active and well five years later. The other patient was a boy of 17 with very numerous polypi in the rectum. After a stormy convalescence he made a good recovery, but for over a year after operation was bothered by very frequent bowel action, twelve to fourteen daily, though he was never incontinent. This has now improved to about eight motions in 24 hours.

The remaining 29 patients were all treated by removal of the colon and anastomosis of the ileum to the rectum. This was either preceded or followed by diathermy coagulation of polypi in the rectum, so that the ileum was anastomosed to bowel free of polypi. One patient died as a result of the operation. Another subsequently died in another hospital as a result of intestinal obstruction. A third patient developed a carcinoma in the remaining rectal segment. This last case had already been reported by Goligher (1953), the essential features being as follows:—

The patient was a woman of 32 who, in February, 1950, had a colectomy and ileorectal anastomosis carried out for polyposis associated with a carcinoma in the sigmoid colon. After recovery from the operation

the polyps remaining in the rectum were fulgurated, and thereafter she attended regularly for examination and fulguration of any fresh polyps. In December, 1951, the rectum was clear, but when she next attended in March, 1952, a small hard ulcer was found on the posterior wall of the rectum, which biopsy proved to be a carcinoma. She was re-admitted for excision of the rectum and ileostomy, but unfortunately died as a result of this operation, which was found to be technically unusually difficult.

It is very satisfactory to be able to record that 26 of the 29 patients treated by ileorectal anastomosis are alive and well at the present time. Most of them have two or three semi-formed bowel actions a day, but no urgency of defæcation. They attend at regular intervals for examination and fulguration of any polypi that may have subsequently developed in the rectum. The intervals at which such visits are necessary varies, being dependent on the findings at each sigmoidoscopic examination.

CHOICE OF SURGICAL TREATMENT

From what is now known about the natural history of colonic polyposis it is only to be expected that operations in which any large part of the colon was retained would be followed by a high incidence of fresh primary carcinomas in the remaining bowel. This has been entirely borne out by the experience of this hospital, as is demonstrated by *Table I*. Looking back to the pre-war period we must not forget that the risk of total colectomy was considerable, the technique of bowel anastomosis in the pelvis was not so well established as at the present time, and that the burden of an ileostomy (before the advent of adhesive bags) was formidable. More recent experience in the last ten years has shown that removal of the colon in one stage can be done with a low mortality (*Table II*), whether an anastomosis of remaining ileum to rectum or anus concludes the operation, or whether an ileostomy is established. This being so we now consider that once the decision to operate has been taken, removal of the whole colon is advisable, even though polypi may still be small and scattered. Limited resections do not give an equal degree of safety from the risk of malignant disease, and though no patient in this series has developed a carcinoma in the right colon, several such cases have been reported by others. Moreover, little advantage would accrue from retention of the right colon, for with modern appliances an ileostomy is no more trouble to the patient than a transverse colostomy. We know that persistent ill health and anæmia may result from slight constant blood-loss from polypi in even a short segment of colon, for it occurred in one patient of this series until the right colon was removed.

The question naturally arises as to whether retention of any part of the large bowel mucosa is advisable, and whether any attempt should be made to adopt surgical procedures which allow the patient to retain rectal control. It might seem that this problem could be solved if the whole colon and rectum were removed, and the ileum anastomosed to the anus, a total procto-colectomy with ileo-anal anastomosis. This has been tried, but our experience with this operation both in polyposis and in other conditions has not shown this to be a satisfactory compromise for two reasons: First the operation is technically more difficult and carries a greater risk; secondly, after this operation rectal control is not always satisfactory—for instance two young people who underwent this operation (one of whom is mentioned in Series II) had an initial period of intense frequency of bowel action, which slowly improved, but they still have six to eight motions daily. We know of two other patients with ulcerative colitis who were incontinent following this operation and who required an ileostomy within a few weeks. This experience with ileo-anal anastomosis agrees with that of other centres where results have been disappointing; Best (1952) has written an excellent account of this operation, with a review both of his own results and those of other surgeons, and states that in only 50 per cent of cases are results satisfactory. While he admits the operation to be feasible and perhaps indicated in selected cases, he has found the trials and complications of the early weeks so discouraging and trying to both patient and surgeon that he says: "I have difficulty in convincing myself that facing the issues described is worth the sweat and tears to both patient and surgeon." Further experience with the operation in the future may lead to improvements which will alter this view.

In the meantime there seem to us to be only two alternatives in most cases of polyposis, either to excise the whole large bowel and establish a permanent ileostomy or to preserve part of the rectum and join the ileum to it. Experience has shown that this second alternative consistently provides satisfactory rectal function, but of course the first alternative is always necessary in those patients in whom a carcinoma of the rectum is present. It may also be necessary for patients in whom the polypi are so numerous in the rectum that diathermy destruction of them all would be liable to result in much scarring and subsequent stenosis. In some cases of this sort, however, it is often possible with care and patience to destroy all the rectal polypi without any stenosis resulting, so that rectal preservation becomes possible.

Preservation of the rectum by ileorectal anastomosis certainly involves a risk that a fresh carcinoma may form later in the remaining rectal segment, and in order to reduce this the patient must be kept under supervision for the rest of his life so that any benign polypi that form may be destroyed before malignant change occurs in them. However, many of these patients only need to be sigmoidoscoped at intervals of a few months and can, apart from this, live unrestricted lives.

The objection that a fresh carcinoma might form in spite of adequate supervision, as happened in one patient of this series, is much more serious. Reports of similar occurrences have appeared in the literature (Swinton and Holt, 1951; Mayo, DeWeerd, and Jackman, 1951), and some American authors for that reason condemn any operation which preserves rectal mucosa. We believe that the policy of conserving the rectum is justified for the following reasons:—

1. The risk of carcinoma arising under adequate supervision is probably small. It has happened to 1 patient of this hospital out of 27 such patients operated upon and still alive, though the interval

since operation is short in many of these. The risk would be much increased in any patient unable or unwilling to attend regularly.

2. The very natural dislike of patients for the idea of an artificial opening for the bowel deserves particular attention in this disease where symptoms are usually mild until the onset of malignancy. If the results of treatment are to improve still further the disease must continue to be treated before malignancy occurs, and to achieve this it is essential that the relatives of affected individuals should come forward for examination and treatment when they are young and practically free of symptoms. They will be reluctant to do this if they think that a permanent ileostomy will be necessary should polyposis be found. Many of these patients know of the hereditary nature of the disease and live in dread of it, usually because they believe that a fatal cancer invariably follows. We have found that if patients can be assured that the disease can be treated and cancer prevented by an operation which will leave them with normal control, then they will be more willing to come forward for examination, and so more patients will come to operation before malignant change occurs.

3. It must not be forgotten that ileostomy itself has its own special complications apart from its social disadvantages. Cattell (1953) has reported a late mortality of 3·2 per cent in cases of ulcerative colitis treated by total procto-colectomy and ileostomy, and the experience of this hospital is similar. It is unlikely that operations involving an internal anastomosis would carry such a high late mortality as this.

For these reasons it seems to us entirely justified to rely on ileorectal anastomosis and to retain the rectal segment where possible, thus accepting the risk of the subsequent development of carcinoma, while doing everything possible to prevent that occurrence. Similar views have been expressed by Mayo and others (1951) in their review of cases treated at the Mayo Clinic.

If it is accepted that a case of polyposis is to be treated by colectomy and ileorectal anastomosis, certain other questions arise which should now be discussed. The first is—"at what age should the operation be carried out"? There can be no one answer to this question, but there are records at this hospital of two patients with polyposis who developed carcinoma at the age of twenty and cases of cancer in polyposis have been reported at an even younger age than this. Since the development of a cancer below the age of 18 is very rare, it would seem that sometime in the patient's teens is usually the best period because then there is still minimal risk of cancer, and yet physical and psychological fitness for major surgery. Three recent patients in this series have had the operation in their early teens, and the smoothness of their post-operative course and quick return to normal bowel action have been very striking. The tendency at this hospital now is to operate at an earlier age than formerly.

The second technical problem concerns the level at which the anastomosis should be done. The shorter the rectal stump the smaller is the chance of polypi forming, and the easier they are to destroy. One of the earliest patients treated here by colectomy with rectal preservation (in 1918) had an ileosigmoid anastomosis; the retained large bowel was not all within reach of the sigmoidoscope, and she later developed a carcinoma of the retained sigmoid colon (*see Table I*). The risk of carcinoma arising is certainly greatest in the rectum and most distal colon and if any of this part is to be retained it is essential that it be easily accessible for endoscopic treatment.

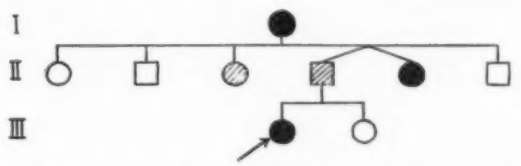


FIG. 574.—Family chart of Mrs. G., who is marked with an arrow in Generation III. *Symbols*: Squares, males; Circles, females; Shaded, polyposis; Black, polyposis + intestinal cancer.

However, satisfactory rectal function requires a length of 8 cm. or more of rectum (measured from the anal verge), and furthermore the very low anastomoses in the pelvis are technically more difficult and carry a greater hazard. Hence it has been the usual practice here in recent years to make the anastomosis between 10 and 12 cm. from the anal verge; this is usually just below the sacral promontory, and this appears to be a satisfactory compromise, allowing an easy anastomosis and good rectal function, with an accessible rectal segment. It is wiser to keep close to the rectal wall in any dissection necessary over and below the sacral promontory so as to avoid any risk of damage to pelvic nerves.

Further points that deserve consideration are the danger of delaying the operation and the risk of implantation of malignant cells. It is difficult if not impossible in many cases to determine either by sigmoidoscope or X rays whether malignant change has occurred, and therefore operation should not be unduly delayed if the age of the patient and the condition of the bowel suggest that the possibility of malignant change is considerable. In any patient over 25 in whom large congested polyps are seen we consider it would be better policy to operate without delay. Further, it is known that exfoliated cancer cells may implant on a raw surface and on granulation tissue (Lloyd-Davies, 1948), and it would therefore seem unwise to fulgurate the polyps in the rectum before the colectomy unless the possibility of a carcinoma more proximally has been excluded with reasonable certainty, for malignant cells may implant from above on the ulcer so formed. It is quite a simple matter to destroy the polyps near the cut edge of the rectum from the abdomen at the time of the ileorectal anastomosis, and when the patient is convalescent to destroy those more distally through an operating sigmoidoscope. This order is probably the safer one for patients seen for the first time in the late twenties or older, preliminary fulguration and later colectomy being reserved for younger people and those with mild disease.

The frequency of follow-up examinations after colectomy with ileorectal anastomosis must vary with the needs of each case. Observation should be frequent for the first year, and at the end of this time

the surgeon will have a good idea how quickly any individual patient tends to form fresh polypi, and the interval between visits can be varied accordingly. Most of our patients are told to attend every three or four months. At each visit care must be taken to get a clear view (by means of a wash-out if necessary) and to examine particularly the posterior wall, which lies in the sacral hollow and is often the most difficult part to see. In some cases occasional admission to hospital for one night may be advisable so that a thorough washout can be given and the operating sigmoidoscope passed under anæsthesia. Although not many patients have so far been followed for many years, we are forming the impression that there may be a tendency for fewer polypi to develop with advancing years, and that longer intervals between visits gradually become permissible. We feel that the experience so far gained justifies the continuation of the policy of surgical treatment in the premalignant phase of the disease by an operation which removes the colon and yet avoids colostomy or ileostomy and preserves normal rectal control.

FIG. 575.—Close-up photograph of tumour in the region of the splenic flexure, removed from Mrs. G. Microscopical examination showed this to be an early carcinoma.

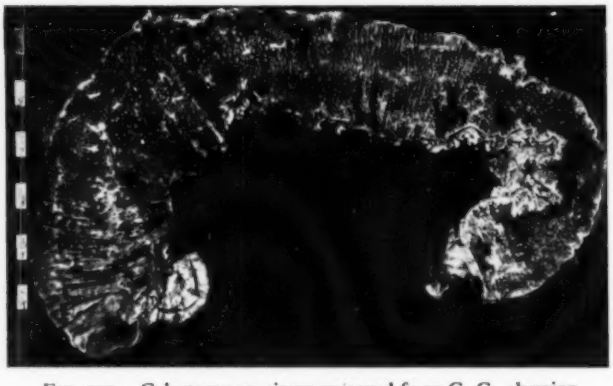


FIG. 577.—Colectomy specimen removed from G. C., showing the large number of polyps present.

ILLUSTRATIVE CASES

Case 1.—The first case has been chosen to illustrate the necessity of keeping in contact with affected members even when they do not complain of symptoms. It concerns Mrs. G. who is marked by an arrow in the family pedigree recorded as *Fig.* 574.

Nine adult members of this family are recorded. So far there have been 5 cases of polyposis, 3 of which were followed by intestinal cancer. Mrs. G's father, two aunts, and grandmother were affected. Her father had a twin sister and both the twins developed polyposis at the same age, and both died after a colectomy operation. A carcinoma was present in the operation specimen removed from the twin sister.

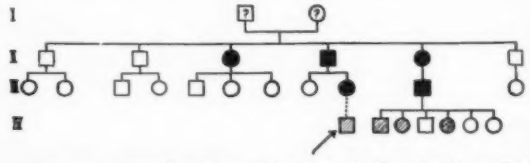


FIG. 576.—Family chart of the boy G. C., who is marked by an arrow in Generation IV. *Symbols*: Squares, males; Circles, females. Shaded, polyposis; Black, polyposis + intestinal cancer.

Mrs. G. is now 32 years of age. She was first examined at the age of 14 by Mr. C. Naunton Morgan in the Out-patient Department of St. Mark's Hospital, and found to have adenomatous polyps in the rectum. She was treated regularly by fulguration over a period of six years and then married and failed to attend. Owing to change of name and of residence the hospital follow-up department lost touch with her for eleven years, but she was eventually traced and persuaded once more to attend. She was then 31 years of age and appeared to be in good health and had no complaint which could be attributed to polyposis, but sigmoidoscopy still showed a few adenomatous polyps in the rectum and a barium enema examination revealed an obstructive lesion in the splenic flexure suggestive of a tumour. Because of this Mr. C. Naunton Morgan decided to carry out a colectomy and ileorectal anastomosis in spite of the almost complete absence of symptoms. Examination of the operation specimen confirmed the presence of adenomatous tumours throughout the colon and of a large villous papilloma type of growth in the region of the splenic flexure

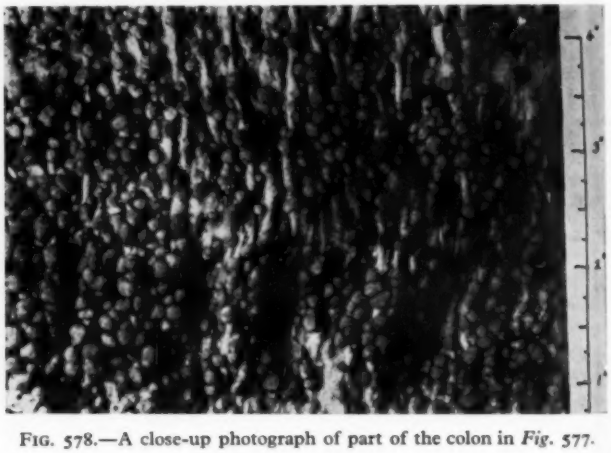


FIG. 578.—A close-up photograph of part of the colon in *Fig.* 577.

(*Fig.* 575). Sections through this tumour showed a small focus of carcinoma, at an early stage of development. The story of this patient emphasizes the importance of keeping in touch with affected members even when they profess to be in good health, and illustrates the fact that malignant disease may arise in the absence of any symptoms due to the polyposis.

Case 2.—The second patient was a boy, aged 17, marked by an arrow in the family pedigree (*Fig.* 576) in which 24 adult members are recorded. Nine of these are known to have inherited polyposis and 5 have died from intestinal cancer.

This family was first investigated by Mr. Tom Rowntree in 1950, and the information available at that time was published (Rowntree, 1950), but in this earlier version of the family pedigree the patient now being reported was not included because at that time he had not been traced and his existence was unknown to us. We knew that his mother had died of rectal cancer at the age of 22, but only subsequently did we discover that she had had an illegitimate son who had been brought up by in-law relatives. This boy at the age of 17 began to have diarrhœa, which was investigated by barium meal, and polyposis coli was discovered. His doctor then referred him to this hospital, where the diagnosis was confirmed, and inquiry into his family connexions showed the linkage with the family previously investigated.

When first examined at St. Mark's Hospital G. C. was 17 years of age. He appeared healthy and his only complaint was persistent diarrhœa for the last six weeks, unaccompanied by blood or excess of mucus. Sigmoidoscopic examination revealed large numbers of adenomatous polyps in the rectum, which were treated by fulguration in several sessions. Then the rectum having been cleared of polyps, colectomy and ileorectal anastomosis was carried out.

The colon from this patient is illustrated in *Fig.* 577 and a close-up of one region in *Fig.* 578. It will be seen that the mucosa was thickly carpeted with rounded adenomatous tumours. In some regions more than thirty tumours were visible in a square inch. An estimate of the total number of tumours calculated from the average density and surface area gave a figure in excess of 5000. The histological picture was that of adenomas undergoing active epithelial proliferation but with no indication of malignancy. This second case illustrates the importance of keeping in touch with a polyposis family, and of taking responsibility for the examination of relatives.

SUMMARY

A review is presented of a series of 60 cases of familial polyposis coli treated by major surgery at St. Mark's Hospital between the years 1918 to 1954 inclusive.

For purposes of analysis we have presented these cases as two series, the earlier one consisting of the 21 cases treated between 1918 and 1945, and the later one consisting of 39 cases treated between 1946 and 1954. The change in the main methods of treatment and the reduction in operative mortality is thus illustrated.

The method of treatment most frequently used at present at St. Mark's Hospital is the removal of the colon with preservation of the lower rectum, to which the ileum is joined—that is, a total colectomy with ileorectal anastomosis. Certain technical points in the performance of this operation are discussed.

Two cases are described which illustrate some of the points mentioned.

We acknowledge with gratitude a grant from the British Empire Cancer Campaign to carry some of the expenses in connexion with this research, which has been made possible by the continued support from this source over a period of many years.

REFERENCES

BEST, R. R. (1952), *J. Amer. med. Ass.*, **150**, 637.
CATTELL, R. B. (1953), *Proc. R. Soc. Med.*, **46**, 1021.
DUKES, C. E. (1952), *Ann. Eugen., Lond.*, **17**, 1.
GARDNER, E. J. (1951), *Amer. J. hum. Genet.*, **3**, 167.
GOLIGHER, J. C. (1953), *Proc. R. Soc. Med.*, **46**, 626.
LLOYD-DAVIES, O. V. (1948), *Ibid.*, **41**, 822.
MAYO, C. W., DEWEERD, J. H., and JACKMAN, R. J. (1951), *Surg. Gynec. Obstet.*, **93**, 87.
ROWNTREE, T. (1950), *Proc. R. Soc. Med.*, **43**, 686.
SWINTON, N. W., and HOLT, J. H. (1951), *Surgical Practice of the Lahey Clinic*. Philadelphia: W. B. Saunders Co.

PAGET'S DISEASE OF THE NIPPLE
A CLINICAL REVIEW OF 27 CASES

BY PERCY HELMAN
FORMERLY RESIDENT SURGICAL OFFICER, ROYAL CANCER HOSPITAL, LONDON
AND MURRAY KLIMAN
DEPARTMENT OF SURGERY, POSTGRADUATE MEDICAL SCHOOL, HAMMERSMITH HOSPITAL, LONDON

THE object of this paper is to review and describe the follow-up findings of 27 cases of proven Paget's disease of the nipple. The cases were seen and treated at the Royal Cancer Hospital, London, and the Postgraduate Medical School of London, Hammersmith Hospital, respectively.

HISTORICAL SKETCH OF THE PATHOLOGY OF PAGET'S DISEASE OF THE NIPPLE

In reviewing the literature one is struck by the vast amount that has been written about the aetiology and pathology of this condition and at the same time one is perhaps justifiably surprised at the very few papers that deal with it from a purely clinical stand point.

Eighty years ago Sir James Paget (1874) described 15 cases of this disease. He wrote that "certain chronic affections of the skin of the nipple and areola are often succeeded by the formation of scirrhous cancer in the mammary gland". In every case he observed, the eruption resisted all the treatment available and cancer of the mammary gland followed within a year to two years. He also remarked that the cancer was always situated in the

substance of the mammary gland and not in the diseased part of the skin. For an explanation of this peculiar occurrence he offered the suggestion that ground for cancer to develop. Darier (1889, 1920) was the first to describe the typical Paget's cells, and believed the condition to be of parasitic origin.

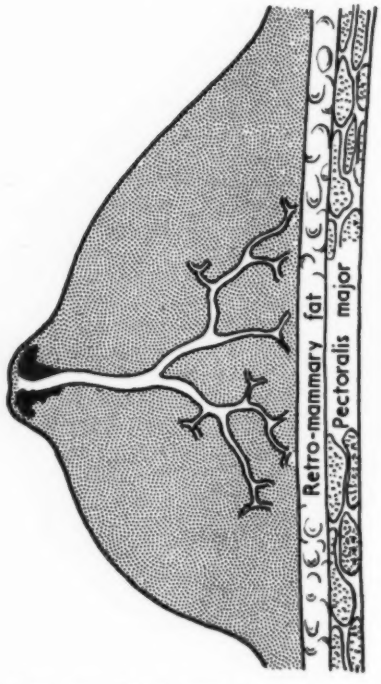


FIG. 579.—Initial stage, showing nipple lesion only.

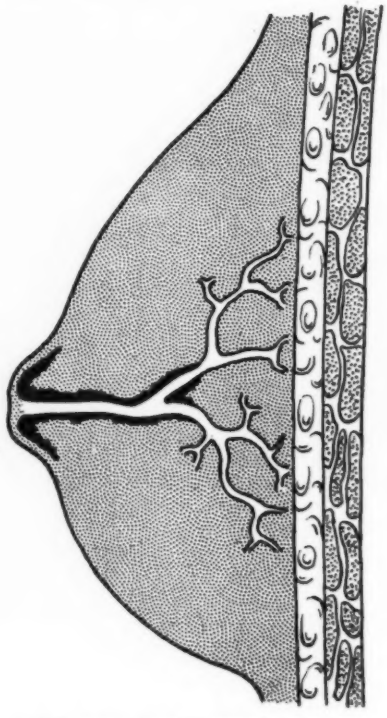


FIG. 580.—Further stage in progress of lesion, showing spread into ducts and acini.

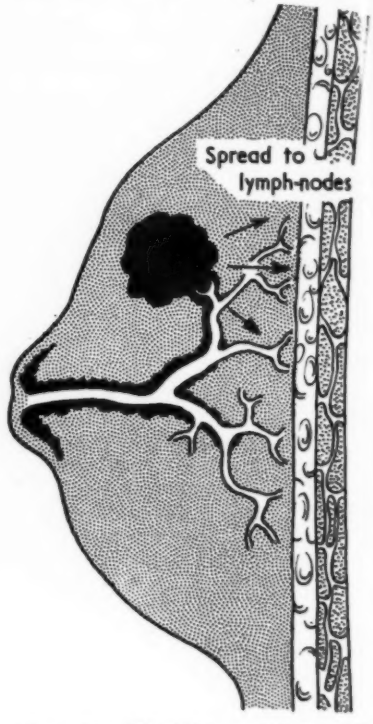


FIG. 581.—Skin lesion, and downward spread with break through into breast connective tissue.

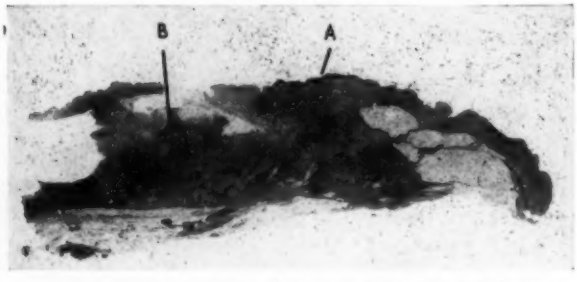


FIG. 582.—Low-power view of a section through tumour and nipple. The flattened nipple with the thickened epidermis lies on the right of centre (A). The tumour lies on the left (B). In the intervening area of breast tissue the ducts can be seen to be filled with intra-duct tumour. (H. and E.) (× 0·84.)

the superficial disease "induces in the structures beneath it, in the course of many months, such degeneracy as makes them apt to become the seat of cancer". From his experience of these cases he suggested that the affected portion should be removed to prevent the later occurrence of cancer.

The first microscopical study of this disease was by Butlin (1880), who in 1876 studied two affected breasts, and concluded that the slight surface area of the disease could induce considerable changes within its substance. While Thin in 1881 thought that the carcinoma was the precursor of Paget's disease, Unna (1896) in 1894 believed that the skin lesion was neither eczema nor cancer, but a degenerative process of the prickle-cell layer, which prepared the

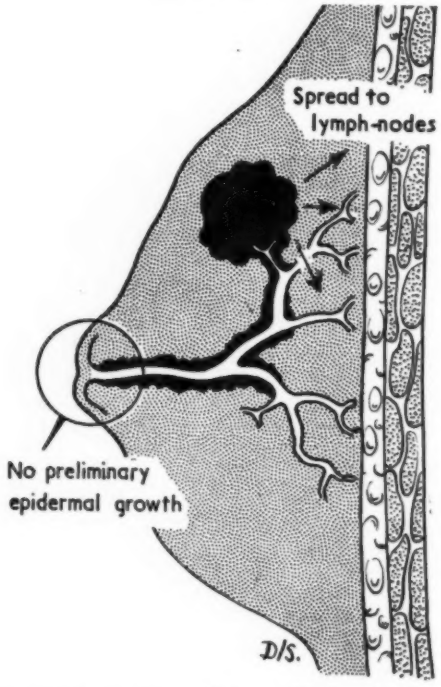


FIG. 583.—Unusual type of lesion, with spread into breast tissue, but with minimal skin changes.

Jacobeus (1904) considered the condition to be a carcinoma from the outset, arising from the glandular epithelium of the ducts. He was the first to implicate

Table I.—DETAILS OF 27 CASES

CASE AND HOSPITAL NUMBER	AGE	DURATION OF SYMPTOMS	PRESENTING FINDINGS	LUMP PALPABLE	ASSOCIATED DISEASE	PATHOLOGY	TREATMENT	FOLLOW-UP
1 M. H. C 2987/46	67	3 yr.	Nipple replaced by eczema 9 × 7 cm. Axilla normal	No	Previous breast abscesses	Intra-epidermal carcinoma	Simple mastectomy followed by deep X-ray therapy	Alive and well 2½ yr. later
2 I. R. R. 2 9/39	61	3 yr.	Eczema left nipple 4·5 × 3·5 cm. Axilla normal	No	Nil	Intraduct carcinoma	Simple mastectomy	Alive and well 14 yr. later
3 I. S. W. 202/39	60	3 yr.	Nipple lesion for some months. Healed — broke down after 3 years. Involved nodes axilla	Upper outer quadrant. Mobile	Nil	Adenocarcinoma. Glands involved	Radical mastectomy followed by deep X-ray therapy	Died 30 mth. later from secondaries
4 J. S. J. 578/43	70	1½ yr.	Eczema left nipple 2 × 2 cm. Involved node axilla	Upper outer quadrant. Mobile	Nil	Scirrhus carcinoma. Glands involved	Radical mastectomy	Died 7½ yr. later from secondaries
5 I. G. S. 24/43	59	1 yr.	Ulcerated area left areola. Healed on many occasions. Axilla normal	No	Nil	Intraduct carcinoma	Simple mastectomy	Alive and well 11 yr. later
6 B. P. 852/42	71	6 mth.	Ulcerated right nipple. 2 × 2 cm. Axilla involved	Upper outer quadrant. Fixed 2·5 cm.	Nil	Biopsy showed Paget's of epidermis of nipple	Deep X-ray therapy only	Died 1 yr. later from secondaries
7 K. G. 000195/45	63	1½ yr.	Eczematous ulceration right retracted nipple. Axilla normal	Upper outer quadrant tethered to skin 5 cm. diameter	Left radical mastectomy for cystic mastitis 20 yr. previously	Scirrhus carcinoma. Nodes not involved	Radical mastectomy followed by deep X-ray therapy	Died from secondaries 22 mth. later
8 I. S. McR. 865/29	70	4 yr.	Red and scaling nipple as well as large area of breast skin involved. Axilla normal	No	Nil	Spheroidal-cell carcinoma	Radical mastectomy	Died 34 months later from secondaries
9 R. O'D. 012894/50	71	3 mth.	Right nipple replaced by eczema 2 × 2·6 cm. Axilla normal (*see Fig.* 584)	No	Nil	Intraduct carcinoma. No extraduct carcinoma. Intra-epithelial cells tend to form tubules (*see Fig.* 585)	Simple mastectomy	Alive and well 3 yr. later
10 I. T. 321/44	64	1 yr.	Area of eczema of nipple. Axilla normal	No	Diabetes mellitus	Intraduct carcinoma	Simple mastectomy followed by deep X-ray therapy	Alive and well 8 yr. later
11 A. H. 010051/49	61		Routine examination showed superficial ulceration left nipple. Axilla involved (*see Fig.* 586)	Upper inner quadrant 4 cm. diameter	Right radical mastectomy 9 mth. previously for carcinoma (anaplasty). Diabetes mellitus	Biopsy showed Paget's disease	Biopsy and deep X-ray therapy	Died 17 months later from secondaries
12 M. K. 007236/48	74	6 mth.	Eczema right nipple, retracted and crusting 1·5 cm. diameter	No	Nil	Paget's nipple. Axilla normal	Simple mastectomy	Alive and well 5 yr. later
13 M. T.	55	3 yr.	Nipple replaced with pale brown superficial ulceration, 3 × 2·8 cm.	No	Nil	Intraduct carcinoma. Axilla normal	Radical mastectomy	Alive and well 3 yr. later
14	74	2 mth.	Ulceration of right nipple 0·5 cm.	No	Rodent ulcer of face	Intra-epidermal Paget's disease	Excision biopsy followed by deep X-ray therapy	Alive and well 1 yr. later

Table I.—DETAILS OF 27 CASES—*continued*

CASE AND HOSPITAL NUMBER	AGE	DURATION OF SYMPTOMS	PRESENTING FINDINGS	LUMP PALPABLE	ASSOCIATED DISEASE	PATHOLOGY	TREATMENT	FOLLOW-UP
15	57	2 mth.	Eczema of right nipple. Palpable node right axilla	Upper outer quadrant	Nil	Intraduct carcinoma. Spheroidal-celled carcinoma in breast	Radical mastectomy followed by deep X-ray therapy	Died from secondaries 4½ yr. later
16 A. C. 19252/48 P. G.	57	1 yr.	Superficial ulceration left nipple. Axilla normal	No	Pernicious anæmia	Paget's nipple	Simple mastectomy, preoperative deep X-ray therapy	Alive and well 4½ yr. later
17 H. G. 147039/52 P. G.	68	2 yr.	Eczema and retracted left nipple. Axilla normal	No	Mitral stenosis	Intraduct carcinoma	Excision biopsy followed by deep X-ray therapy	Alive and free from secondaries 10 mth. later
18 L. B. 125096/51 P. G.	60	3 mth.	Eczema right nipple. Axilla normal	No	Nil	Intraduct carcinoma	Simple mastectomy followed by deep X-ray therapy	Alive and well 2 yr. later
19 A. L. 133515/52 P. G.	33	2¾ yr.	Eczema right nipple with superficial ulceration. Axilla normal	No	3 mth. pregnant	Intraepithelial carcinoma	Radical mastectomy	Alive and well 2½ yr. Pregnant again
20 B. B. 768/39 P. G.	50	4 yr.	Recurring eczema right nipple. Node in axilla	Upper outer attached to pectoralis fascia	Nil	Scirrhus carcinoma in breast	Radical mastectomy followed by deep X-ray therapy	Died from metastases 8 mth. later
21	52	1 yr.	Erosion right nipple. Node right axilla	Upper outer quadrant tethered to skin 3 × 2 in.	Carcinoma left breast 1 yr. later	Scirrhus carcinoma	Radical mastectomy followed by deep X-ray therapy. Deep X-ray therapy only for left breast	Died from secondaries 16 mth. later
22 B. S. 17787/41 P. G.	49	18 mth.	Scaly red nipple left 1 cm. diameter. Axilla normal	Inner quadrant	Hypertension	Scirrhus carcinoma	Radical mastectomy	Died 5 yr. later from secondaries
23 A. P. 90864/48 P. G.	75	3 yr.	Nipple destroyed by eczematous, weeping scaly skin	No	G.U. cleft palate. Congestive cardiac failure	Intraduct carcinoma	Deep X-ray therapy, very poor general health (also excision biopsy)	Died from congestive cardiac failure soon afterwards
24 E. G. 150850/53 P. G.	70	9 mth.	Ulcerated right nipple 1½ cm. diameter node axilla	Mass 5 cm. deep to nipple	Nil	Extraduct carcinoma simplex axilla. Node involved	Radical mastectomy	Alive and well 6 mth. later
25 M. C. 17282/37 P. G.	35	3 yr.	Ulcerating area 2 cm. of right nipple with serous discharge. Axilla clinically free from disease	Upper outer quadrant. Mobile	Nil	Intraduct carcinomatous nodule deep in breast. Nodes involved	Radical mastectomy followed by deep X-ray therapy	Died from secondaries 4½ yr. later
26 H. A. 77777/47 P. G.	73	2 yr.	Ulcerated nipple, healing from time to time. Axilla clinically free from disease	No	Nil	Intraduct carcinoma. Nodes free	Radical mastectomy followed by deep X-ray therapy	Alive and well 5½ yr. later
27 B. L. 124482/53 P. G.	71	4 yr.	Right nipple, replaced by ulcerating, weeping area. Right axilla free (*see Fig.* 587)	Lower quadrant tethered to skin	Developed carcinoma left breast 1 yr. later	Extraduct carcinoma	Simple mastectomy followed by deep X-ray therapy	Alive 1 yr. later, but now has carcinoma of left breast and secondaries in chest

intraduct cancer in the aetiology of this disease. The changes in the epidermis he ascribed to proliferation of the glandular cancer within the epithelium. Handley (1919) stated that the skin changes were " nutritional and non-malignant " as a result of the filling of the corium and subcutaneous tissue lymphatics with cancer cells which originate in the deeper ducts and acini. Cheatle (1923, 1930) said that the skin lesion of the nipple was carcinoma, that the carcinoma within the breast substance was a primary carcinoma of the breast epithelium, and that the agent of irritation which induced the skin lesion was also concerned in inducing the primary carcinoma in the epithelial cells of the breast.

In his thesis on Paget's disease of the nipple, Inglis (1936) sets out very clearly his theory as to its nature, origin, and mode of spread. He believes it to be a malignant process from the outset, commencing at the junction of the lactiferous duct with epidermis. From this area there is a continuous spread downwards in the epithelial lining of the duct wall and also outwards within the epidermis of the nipple. The downward spread in the duct is in the form of a hollow cylinder, not in the form of a solid column, so that it presents a ring of neoplastic cells in the substance of the epithelial lining, the lumen of the duct containing merely a little secretion. This may explain why a blood-stained discharge from the duct in this disease is so very uncommon.

Paget's cells according to Inglis are cancer cells that have extended from the ducts within the confines of the surface epithelium without breaking through into the subjacent connective tissue.

Muir (1927, 1939) wrote extensively of the pathology of Paget's disease. He agreed with Inglis that the skin lesion was a result of intra-epithelial growth from an intraduct carcinoma, but felt strongly that the cancer of the connective tissue of the breast was not merely a result of extension downwards from the primary lesion near the mouths of the lactiferous ducts. He brought strong histological evidence to show an upward spread in the duct (to the surface) and also stated that he could demonstrate normal duct tissue between the breast cancer and the surface lesion. He postulated that the growth was ordinarily due to extension from an independent focus of intraduct carcinoma.

To sum up then, as far as the clinician is concerned, Paget's disease is a malignant process from the outset. The first lesion is an intraduct carcinoma and extension of this to the epidermis produces the scaly, red eczema of the nipple and areola. As far as one can tell, this then appears to be a very early stage—a stage which is curative if the whole breast is removed. One stage further means a break through from the purely intraduct condition to a growth invading the breast connective tissue, and this is a late stage which is not usually curative.

The clinical progress can best be illustrated by the diagrams (*Figs.* 579–583).

Fig. 579 shows the condition as first seen in the majority of cases. The skin lesion is caused by the spread of cancer cells from the mouths of the lactiferous ducts.

Fig. 580 shows a stage farther in its progress, the spread farther down the ducts or acini, but still no outward break through into breast substance. The condition may remain like this for a few years.

Fig. 581 shows the skin lesion and downward spread with a break-through into the breast connective tissue, later to form a palpable lump. At this stage the spread of the disease may preclude curative treatment.

Fig. 582 shows a section through tumour and nipple at the same stage as illustrated in *Fig.* 581. The tumour can be seen separated from the nipple lesion by normal breast tissue. The ducts are involved by cancer cells. *Fig.* 583 shows an unusual type with marked spread down the duct and into the breast tissue, but with minimal skin changes. In this type there are no naked-eye skin changes, but a palpable breast lump. Histological examination of the nipple will reveal the presence of Paget cells.

CLINICAL FEATURES OF THE 27 CASES

All the cases were female (*Table I*). There are, however, reports of Paget's disease of the nipple occurring in male patients (Zarattini, 1943; and Rubinstein, 1930).

Age at Onset.—The ages of the patients in this series vary from 31–75 years (*Table II*).

Table II.—Age at Onset of Disease

Years	*Cases*
31–40	2
41–50	2
51–60	10
61–70	8
71–80	5

This compares almost exactly with 29 cases tabulated by Costello (1945), and follows the normal age distribution of carcinoma of the breast as reported in the Clinical Statistical Report of the Royal Cancer Hospital, 1945–9.

The incidence of the disease appears to be under 1 per cent of all carcinomas of the breast. Dockerty and Harrington (1951) found the incidence in their series to be 0·7 per cent.

Table III.—Duration of Symptoms

	Cases
Less than 6 months	6
6 months–1 year	5
1–2 years	6
2–3 years	7
3–4 years	3

There does not seem to be any relationship between the duration of symptoms (*Table III*) and the survival time. One patient gave only a six-months' history but died with secondaries within one year (*Case* 6). On the other hand, another patient giving a history of one year is still alive and well eleven years later (*Case* 5). The longest history is four years, but the patient concerned died with secondaries within eight months of treatment (*Case* 20).

Side of Lesion.—The right breast was involved in 15 cases. In no case was the lesion bilateral.

Presenting Findings.—

a. Fifteen patients presented with eczema or superficial ulceration of the nipple only.

b. Eleven patients presented with eczema as well as a palpable lump.

c. One patient presented with only a palpable lump of two months' duration and no obvious skin changes.

The Skin Lesion.—The patients stated that they first noticed an ' irritation ' or ' itching ' of the nipple, and this would usually be followed by simple crusting or scaling which either persisted or recurred. In a

FIG. 584.—*Case* 9. Right nipple replaced by eczema. No lump palpable in this breast.

FIG. 586.—*Case* 11. Shows left nipple ulceration. A lump was palpable in the upper and inner quadrant of this breast.

full-blown and obvious case the lesion was described as " weeping, reddish, sometimes granular and discharging serous or sero-sanguineous material, which often would soil the undergarments ".

The lesion always involved the nipple and areola and often spread to the skin of the breast tissue. In no case was blood-stained discharge from the nipple duct recorded.

We stated that the eczema not only persisted but actually sometimes recurred after periods of perfectly normal appearance. To illustrate this, it would be best to quote the following four cases :—

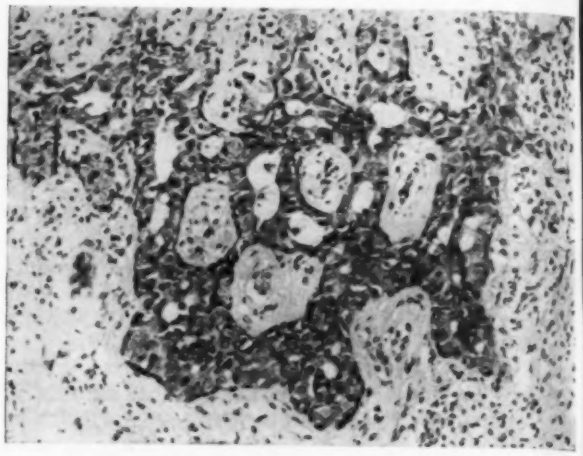


FIG. 585.—*Case* 9. High-power view of the epidermis of the nipple. A partially transverse section of the deeper part. The epidermis is almost completely replaced by tumour cells, which here and there (especially in the centre) form definite tubular luminæ. The original epidermal cells are flattened against the stroma. (H. and E.) (× 235.)

FIG. 587.—*Case* 27. Shows right nipple replaced by ulcerating and weeping area. An adherent lump was palpable in the lower quadrant of the breast.

Case 3.—A woman of 60 complained of soreness of the nipple which started over three years previously. There was an area of redness around the areola and nipple. The lesion quickly healed and remained so for three years. When seen again she not only had a recurrence of eczema, but a palpable breast lump as well (hard and craggy in the upper and outer quadrant). Radical mastectomy was

performed, followed by deep X-ray therapy to the supraclavicular region. She died from secondaries two years later.

Case 5.—A woman of 59 complained of ulceration of the left nipple for one year. This lesion had healed on numerous occasions, but lately had failed to respond to simple measures. There was no palpable lump. A local mastectomy was performed and the patient is still well eleven years later.

Case 20.—A woman of 54 complained of soreness of the right nipple for four years. This lesion responded to simple measures but recurred, and there was now a palpable breast lump. In spite of radical mastectomy and deep X-ray therapy, the patient died from secondaries eight months later.

Case 26.—A woman of 73 complained of ulceration of the right nipple for two years. This had healed from time to time, but did not now respond to simple measures. No lump in the breast was present at the time. Radical mastectomy and deep X-ray therapy were carried out and the patient is alive and well five and a half years later.

The Lump in the Breast.—A lump in the breast was found in 12 cases, presenting in all of them all the features of a malignant growth. In 8 cases the mass was found in the upper and outer quadrant. In 1 case it was situated deep to the nipple and in the others was in the inner half or lower quadrant of the breast.

The following was the staging of these cases: In 3 cases the staging was purely clinical, but in the others it was decided by pathological examination.

Stage 1 (3 cases), i.e., tumour clinically confined to the breast. No nodes palpable.

Stage 2 (5 cases), i.e., same as stage 1, except that involved nodes were found in the axilla on the same side only.

Stage 3 (4 cases), i.e., as above, tumour attached to underlying fascia or muscle.

The Time Relationship of the Onset of Eczema to the Finding of a Breast Lump.—In 1 case a lump was found in the breast within a month of the onset of the skin lesion. In others the interval before detection varied from two months to four years. A large number of the lumps were found without the patient having suspected their presence. There were 4 patients who had eczema for over three years without the development of a palpable lump (*Cases* 2, 8, 13, 23).

Coincident Pathology of the Breast.—One patient had had carcinoma of the other breast treated by radical mastectomy (*Case* 11). Two patients developed carcinoma of the other breast subsequent to the onset of Paget's disease (*Cases* 21 and 27). One patient had had breast abscesses four and thirteen years prior to the onset of the nipple scaling (*Case* 8). One patient was 33 years of age and three months pregnant when the Paget's nipple was discovered; there was no associated palpable breast lump although the disease had been present for nearly three years. This patient is alive and well two and a half years after a radical mastectomy. She is now pregnant again (*Case* 20).

Treatment.—

1. *Those Patients in whom the Nipple Lesion Only was found* (15 *cases*):—

Radical mastectomy: 4 patients; 1 of whom had post-operative irradiation.
Local mastectomy: 8 patients; 3 of whom had post-operative irradiation.
Biopsy excision: 3 patients; 3 of whom had post-operative irradiation.

One patient in this series died of congestive cardiac failure a few weeks after excision biopsy. Another died thirty-four months after a radical mastectomy from secondary carcinoma. All the others are quite well after periods varying from three months to seventeen years.

Alive and well: *Table IV* shows the follow-up of these patients.

Table IV.—Follow-up of Cases presenting with Nipple Lesion only, Alive and Well

	Patients
0- 3 years	5
3- 5 years	3
5-10 years	3
Over 10 years	2

2. *Those who had Paget's Disease with a Palpable Lump in the Breast Tissue* (12 *cases*).

Radical mastectomy: 9 patients; 6 of whom had post-operative irradiation.
Local mastectomy: 1 patient with post-operative irradiation.
Biopsy excision: 1 patient with post-operative irradiation.
Deep X-ray therapy only: 1 patient.

Ten of these patients are dead from metastases. Of the 2 still alive 1 has now presented at the hospital with carcinoma of the other breast and known secondaries one year after treatment. The other patient is well, but has only been followed up for six months.

Follow-up.—*Table V* shows the follow-up of these patients.

Table V.—Follow-up of Cases presenting with Palpable Lump

Years	*Died*
0–1	2
1–3	5
3–5	2
5–7½	1

Seven patients died within three years. Nine patients died after a five-year follow-up and there are no known survivors after seven and a half years.

Table VI.—Survival in the Two Distinct Groups of Patients

Length of follow-up	*No lump*		*Lump*	
	Alive	*Dead*	*Alive*	*Dead*
0–3 years	5	2	2	7
3–5 years	3	—	—	2
5–10 years	3	—	—	1
Over 10 years	2	—	—	—

DISCUSSION

Bloodgood (1924) recorded his observations of 7 cases of what he called Paget's disease of the nipple in which the nipple lesion healed under simple and protective treatment. In fact, he states that carcinoma of the breast in Paget's disease can be preventable. It is interesting to note that he only followed up these cases for a few weeks to three months. Our experience does not bear out his argument. Four of our cases proved that the nipple

lesion can actually heal (or appear to do so) and in 1 case the nipple remained healed for three years. This last patient returned to the out-patient department with not only a recurrence of the nipple lesion, but also a palpable lump in the breast; in spite of radical mastectomy she died from secondaries soon afterwards. An eczematous lesion of the nipple which heals spontaneously can still be a Paget's disease; a biopsy is essential as soon as the diagnosis is suspected.

In the very earliest stages the patient may complain only of some itching or irritation of the nipple. This is usually followed by a redness and scaling, and later by superficial ulceration. It would appear to us that a complaint of irritation of the nipple, even with minimal objective skin change, would warrant a biopsy.

We have divided the patients into two distinct clinical groups :—

1. Those patients who had eczema of the nipple only appear to do well with early surgical treatment. The number in this series is not large enough to show any significant difference in the follow-up of those who had had radical mastectomy as compared with those who had simple mastectomy. The impression one gains, however, is that a simple mastectomy followed by deep X-ray therapy gives as favourable a result as any other treatment. On the whole the prognosis in this group is as good as, or perhaps even better than, the prognosis of Stage I breast cancer.

2. The prognosis in those patients who had a palpable lump in addition to a nipple lesion is very bad, and it appears to us that the presence of a lump in the breast means that disease is advanced. Of the 12 patients recorded, 7 were dead within three years, and 10 were dead within a period of seven and a half years—all from secondary carcinoma, and this in spite of radical operations and/or full courses of deep X-ray therapy.

A clinical differentiation has previously been described by West and Nickel (1942), who described a series of 20 cases. They stated that those patients presenting with eczema of long standing which may or may not be associated with a definite tumour in the breast, had a good prognosis with early surgical treatment, while those who from the first have a carcinoma of the breast with secondary invasion of the nipple, have a bad prognosis. Our follow-up does not quite bear this out. The length of the history of eczema does not appear to be so important in the prognosis. The prognosis seems to be bad only in those cases where there is a palpable tumour of the breast. Treatment of patients who present with a palpable tumour can only be palliative, and it is questionable whether a severe operation such as a radical mastectomy is warranted. Local mastectomy followed by a course of deep X-ray therapy would seem a reasonable procedure for palliation at this late stage.

SUMMARY

1. The clinical features of 27 cases of Paget's disease of the nipple are described.

2. In the follow-up of these cases one finds that the cases are best divided into two clinical groups :—

a. Those cases of Paget's disease of the nipple which present without a palpable breast lump. The prognosis of these patients following treatment is uniformly good.

b. Those cases of Paget's disease of the nipple who present with a palpable breast lump. The prognosis of these patients following treatment is uniformly bad.

3. In many cases the nipple lesions may apparently heal. They invariably break down and recur, even, as in one case, after a period of three years.

Acknowledgements.—Our thanks are due to Professor Ian Aird and Mr. R. W. Raven for advice and criticism; to the surgeons at the Hammersmith Postgraduate and Royal Cancer Hospitals for allowing us to publish their cases; to Dr. J. W. Whittick and Dr. B. Lennox for the pathological reports; to Mr. C. A. P. Graham, of the Photographic Department, who prepared the photomicrographs; to Mr. D. G. Simmonds, who prepared *Figs.* 579–581, 583; and to Miss S. Morgan who typed the script.

REFERENCES

BLOODGOOD, J. C. (1924), *Arch. Surg., Chicago*, **8**, 461.
BUTLIN, H. T. (1880), *Brit. med. J.*, **1**, 128.
CHEATLE, G. L. (1923), *Brit. J. Surg.*, **11**, 295.
— — (1930) *Brit. med. J.*, **2**, Canadian suppl., p. 13.
CLINICAL STATISTICAL REPORT OF THE ROYAL CANCER HOSPITAL (1945), No. 1, 84.
COSTELLO, C. J. (1945), *Arch. Surg., Chicago*, **51**, 262.
DARIER, J. (1889), *C. R. Soc. Biol. Paris*, **1**, 294, quoted by INGLIS.
— — (1920), *A Text-book of Dermatology* (English translation). Philadelphia: Lea & Febiger.
DOCKERTY, M. B., and HARRINGTON, S. W. (1951), *Surg. Gynec. Obstet.*, **93**, 317.
HANDLEY, W. S. (1919), *Brit. J. Surg.*, **7**, 183.
INGLIS, K. (1936), *Paget's Disease of the Nipple*. London: Oxford University Press.
JACOBEUS, H. C. (1904), *Virchows Arch.*, **178**, 124.
MUIR, R. (1927), *J. Path. Bact.*, **30**, 451.
— — (1939), *Ibid.*, **49**, 299.
PAGET, SIR JAMES (1874), *St. Bart's Hosp. med. Rep.*, **10**, 87.
RUBINSTEIN, M. W. (1930), *Arch. Derm. Syph., Chicago*, **22**, 28.
THIN, G. (1881), *Trans. path. Soc. Lond.*, **32**, 218.
UNNA, P. G. (1896), *The Histopathology of the Diseases of the Skin*. Edinburgh: W. F. Clay.
WEST, J. P., and NICKEL, W. F. (1942), *Ann. Surg.*, **116**, 19.
ZARATTINI, A. (1943), *Tumori*, **17**, 136.

OSTEOMATA OF THE PARANASAL SINUSES

A REPORT OF FIVE CASES, WITH SPECIAL REFERENCE TO THEIR TREATMENT

By JOHN ANDREW

DEPARTMENT OF NEUROLOGICAL SURGERY, ST. BARTHOLOMEW'S HOSPITAL, LONDON

Osteomata arising in the paranasal sinuses have long been recognized by clinicians. According to Hewett (1867) the first cases were described over four hundred years ago. Until one hundred years ago these tumours were usually untreated, and sometimes attained very large dimensions, often providing museum specimens. There have been numerous reports of one or a few isolated cases, but Malan (1938) and Teed (1941) have both made an analysis of large groups collected from the literature, and these contain much valuable information. During the present century the cases have usually been reported either by an otorhinologist, an ophthalmologist, or a neurological surgeon. The mode of presentation of the tumour has determined the specialist to whom the patient has been referred, and different specialists have recommended different methods of treatment. In this paper 5 cases of osteomata arising in the frontal or ethmoidal sinuses will be described. The differing presenting symptoms were such as to bring the patient into any of the special fields mentioned above. It is believed that howsoever the tumours occasion symptoms, unless they are very small, their radical treatment should be effected by a transfrontal approach; it is hoped to substantiate this view from the case histories described below. A brief summary of theories concerning their aetiology, pathology, and symptomatology will be presented.

AETIOLOGY

Teed (1941) has drawn attention to the finding that osteomata arising in the paranasal sinuses occur in young people most commonly in the second and third decades. Sex incidence shows a male preponderance. In the present series the age incidence was rather high as 3 of the patients were 45 years of age or over. There were 3 men and 2 women (*Table I*). As an aetiological factor trauma has been cited in most previous reports. Minor injuries to the forehead are frequent, and may therefore be of little significance; however, frontal injuries were recalled by 3 of the 5 patients reported below, and in 2 a tumour appeared shortly afterwards. Infection is also given as a causative factor, but did not appear to be of significance in the present series. A parallel might be drawn with osteomata arising from the mastoid portion of the temporal bone, since a previous history of otitis media is often wanting. Dowling (1945), however, has described 2 frontal sinus osteomata, with coexisting osteitis of the frontal bone above the affected sinus. In each case the area of osteitis was close to the site of attachment of the tumour, and he suggested that either the osteitis or infection in the sinus might have predisposed to the formation of the tumour.

There have been divergent views as to the point of origin of these tumours, some considering that it is the fronto-ethmoidal junction, and others that it is the mucoperiosteum of the sinus in which the osteoma arises. The frequent incidence of the paranasal osteomata in young people led Arnold (1873) to believe that the site of origin might be at the junction of the frontal and ethmoidal bones for, according to Cohnheim's general theory of development, errors in growth are more likely to occur at the junction of two bones, one of which is formed in membrane (frontal) and the other in cartilage (ethmoid). Teed (1941) found that frontal osteomata may have a pedicle attached to any part of the wall of the frontal sinus, and he was therefore unable to support this view. He noted from his review, as also did Malan (1938), that osteomata arose in the frontal sinus more commonly than in the ethmoid, and that the sphenoid and maxillary sinuses were only rarely the site of origin.

Table I.—Sex and Age Incidence

Case	Sex	Age
1	Male	14
2	Female	28
3	Female	48
4	Male	60
5	Male	45

Dolbeau (1871) was among the first to proclaim that these osteomata arose from mucoperiosteum lining the wall of the parent sinus. Fetisoff (1929) made detailed pathological studies of these tumours, producing evidence that they arose from an island of periosteum which he believed had been split off. He put forward the view that there was metaplasia of fibrous into bony tissue in such islands, commencing centrally and spreading outwards, and that any peripheral osteoblastic process was of secondary importance in the formation of the osteomata. Histological study showed that the fibrous tissue surrounding the osteomata was in direct continuation with that filling the interstices of the spongiose bone in the centre of the tumours, and he gave this as additional evidence of their origin from periosteal 'islands'. He believed that either trauma or infection might precipitate this process.

In a recent review Guns (1952) recalled the theory of Tillaux. The latter claimed that the frontal sinus mucosa had on its deep surface a fibrous layer possessing the singular property of ossification. As an osteoma is initially enveloped by the same layer, he believed that the tumour must have developed from this layer, and that it could also increase in size whilst lying free within the sinus. Armitage (1931) has quoted Rokitansky's view that

the periosteum lining the frontal sinus produced cartilage, and that enchondromata were liable to occur. Should these ossify, then they would become osteomata. Other views as to the origin of the growths include ossification in polyps, and bony neoplasms arising in the frontal diploë.

PATHOLOGY

Whilst they are still small the osteomata are spherical or ovoid; as they grow their external configuration becomes a mould of the sinus in which they develop. When large, their surface becomes lobulated. If cut across the tumours may show a grey and white laminated structure, and Hewett (1867) associates the name of Bartholinus, of three hundred years ago, with the superficially descriptive but pathologically misleading term of 'petrified brain', given to these growths. In veterinary circles this term was applied for the next hundred years to the bony tumours found in the frontal sinuses of oxen.

Table II.—History of Preceding Trauma or Upper Respiratory Infection

Case	Trauma	Infection
1	Absent	Absent
2	Absent	Absent
3	Present	Absent
4	Present	Absent
5	Present	Absent

The tumour is initially connected to the wall of the parent sinus by a narrow pedicle, the site of attachment being variable. At a later stage this pedicle may become fractured or obliterated; only one was found in the cases to be described. There is a layer of mucoperiosteum covering the osteoma, which becomes continuous with that lining the parent sinus around the tumour pedicle. In advanced cases the mucous membrane becomes destroyed and the tumour may be covered by a thin layer of fibrous tissue only. Histological examination of the tumour reveals either a compact or spongy osseous structure, although mixed forms are common. A review of the literature has not shown evidence of malignant change in these tumours. As growth proceeds, the osteoma may spread into the adjacent sinuses so that ultimately it may be impossible to establish in which one the tumour originated. The walls of the sinus may become extremely thinned and even destroyed. An osteoma of the frontal sinus may displace the anterior table of the sinus forwards, producing deformity, and ultimately may come into direct contact with the scalp after eroding the anterior table. Backward growth of an osteoma in this sinus may destroy the posterior table, and as the dura mater is firmly attached to the cranial base there is a likelihood of dural erosion, which may result in cerebrospinal fluid rhinorrhœa, pneumocephalus, and intracranial infection. Downward growth may destroy the floor of the sinus, allowing spread of the tumour into the nasal cavity, or, more commonly, into the orbit. In later cases there may be displacement, and even destruction, of the eye.

Spread of an ethmoid osteoma beyond the parent sinus occurs most commonly either through the roof of the sinus into the anterior cranial fossa, where again the dura is in danger of erosion, or laterally into the orbit. An osteoma arising in the maxillary sinus was reported by Hilton (1836). This spread upwards into the orbit, destroying the eye, and after ulcerating through skin, spontaneously separated, leaving the patient with a large ulcer, the crater of which was formed by the orbit and maxillary antrum.

SYMPTOMATOLOGY

(*Table III*)

With the exception of pain, the symptoms occasioned by osteomata of the paranasal sinuses will depend upon the direction and extent of their growth. The duration of symptoms is often surprisingly short in view of the bony nature of the tumours: in the present series this was two years or under in 3 of the cases.

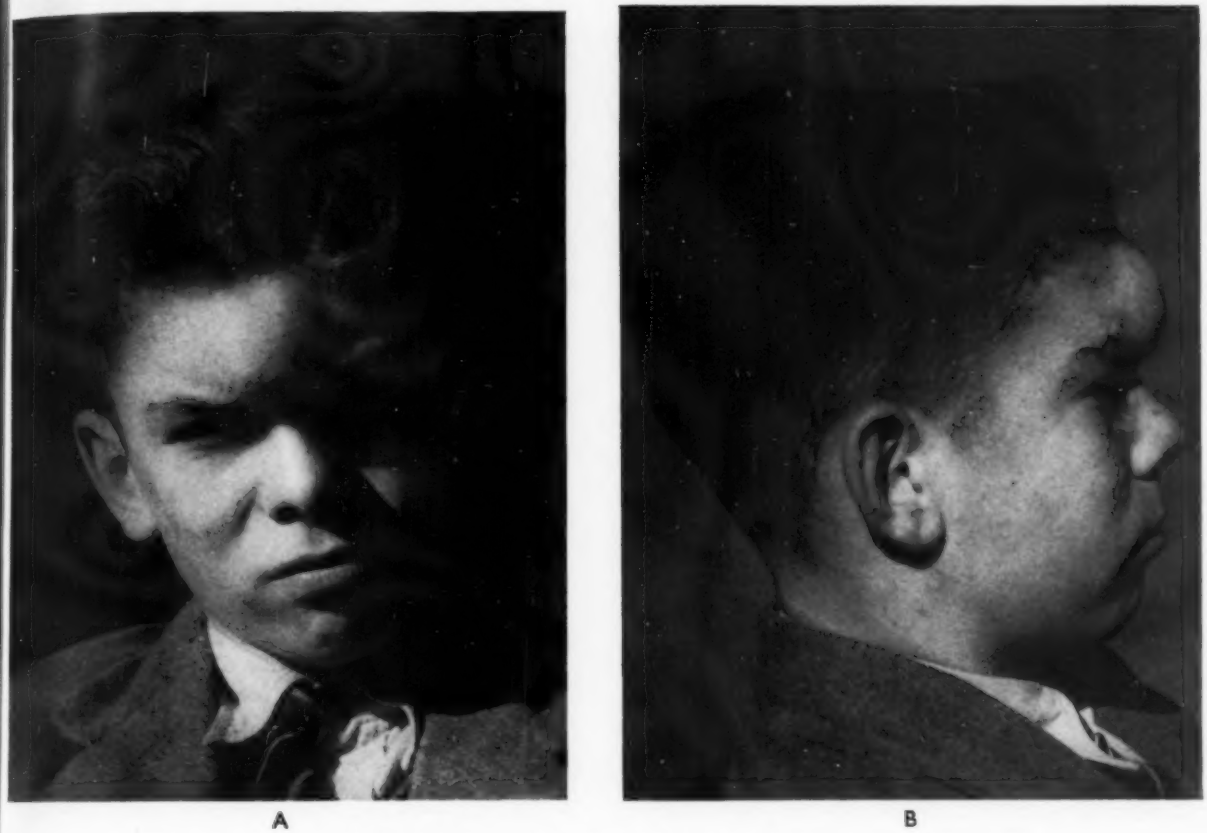
1. Pain.—Pain may be unilateral, either in relation to a visible swelling or behind one eye; alternatively, the patient may suffer from frontal headaches with no lateralizing features. In his extensive review Teed (1941) found pain or headache to be common; and this has been so in many of the smaller series described. *Case* 3 had experienced shooting pains behind her right eye, and *Case* 2 had experienced mild frontal headaches. In neither of these was the pain thought to be due to recurring mucoceles. *Cases* 4 and 5 were free of headache, in spite of long-standing deformity, until their tumours had occasioned acute intracranial infection.

Table III.—Presenting Symptoms

Case	Headache or Pain	Swelling or Deformity	Visual Disturbance	Acute Intracranial Infection
1	−	+	−	−
2	+	+	+	−
3	+	+	+	−
4	+	+	(+)	+
5	+	+	−	+

2. Deformity.—This is the most common presenting symptom, and was found in all of the cases presented below. It may take the form of either a hard bony swelling or unilateral proptosis. An osteoma of the frontal sinus may cause its outer table to be displaced forwards, the tumour therefore presenting just above the glabella. An osteoma arising in the ethmoid air cells or extending into the orbit may produce a bony swelling related to the nasion or to the orbital margins. The bridge of the nose may even appear spread in the late cases. Tenderness is not a feature unless there is an inflammatory change of the overlying superficial tissue; the skin is usually freely mobile over the swelling. Ulceration through the skin is exceedingly

rare and the case of Hilton has already been mentioned. Proptosis is occasioned by the orbital extension of the tumour and is, of course, non-pulsating. It may increase suddenly as a result of orbital cellulitis. The globe of the eye is frequently displaced downwards as well as forwards, particularly when the osteoma arises in the frontal sinus.



A B

FIG. 588.—*Case* 1. Pre-operative photograph to show deformity: A, Frontal view; B, Lateral view.

3. Visual Disturbance.—This will be characterized most frequently by diplopia, and less often by visual loss.

Diplopia will be caused by displacement of the eye, or mechanical interference with its movement by the orbital extension of an osteoma. Paresis of ocular muscles due to nerve involvement must be unusual or late. *Case* 2 described vertical diplopia on upward gaze during examination, and this was due to interference with upward movement of the eye by the overlying swelling.

Visual Failure: *Case* 4 had been blind since adolescence following a blow on the forehead, and the loss of vision was on the basis of bilateral retinal detachment. Even though the osteomata often commence at this age, and may be very slowly growing, the two conditions in this patient were thought to be unrelated. Should blindness occur, it will be primarily unilateral and occasioned either by destruction of the eye from the spread of the tumour, by infection, or by direct pressure on the optic nerve. Parsons (1904) has made reference to large tumours completely destroying one eye. Primary bilateral optic atrophy leading to total blindness from an osteoma arising from the sphenoidal sinus has been recorded by Harrison (1942).

4. Infection.—

Upper Respiratory Tract.—Although Cushing (1927), Armitage (1931), and others have reported cases in which there was recurring upper respiratory infection, no such history was obtainable in this series. The absence of such infections is surprising as pus was found in the frontal sinuses in 3 of the cases at operation. Recurring mucoceles of the frontal sinus have been reported by several authors, and are caused by intermittent obstruction to the drainage of normal secretions; infection in such cases must be common.

More fulminating infections, spreading to all the paranasal sinuses and to the orbit, have been described, and occurred in *Case* 4.

Intracranial Spread of Infection.—This is the most serious complication of these tumours. *Case* 4 developed a pneumococcal meningitis in addition to orbital cellulitis, and *Case* 5 a cerebral abscess. Either acute infection in the paranasal sinuses or the intracranial spread of the tumour may be responsible for this development. Other indications of the tumour eroding the dura are cerebrospinal fluid rhinorrhœa and spontaneous pneumocephalus, the air accumulating in the subdural space, the cerebrum, or in the ventricular system. Such cases have been described by Cushing (1927), Armitage (1931), and Hallberg and Begley (1950). The presence of a cranionasal fistula, whereby air or pathogenic

organisms may readily enter the cranial cavity, will expose the patient to the danger of subarachnoid, subdural, or intracerebral infection.

DIAGNOSIS

Without the presence of a bony swelling the diagnosis may be difficult and must usually rest upon the radiological findings. The appearances are typical—namely, a dense bony tumour occupying and expanding one or both frontal sinuses or the ethmoid cells, with perhaps orbital or intracranial extension. It is noteworthy that in the first case in Cushing's series a tentative diagnosis of an olfactory-groove meningioma had been made, the nature of the lesion remaining obscure until it was exposed by operation.

CASE REPORTS

These are divided into three groups. The first consisted of 1 case and presented with deformity as the only symptom. The second group contained 2 cases, presenting with deformity, visual disturbance and headache. In the third group there were 2 cases which were both admitted to hospital with acute intracranial infection.

Group 1.—

Case 1.—J. T., male, aged 14½. Osteoma of frontal sinus presenting with deformity.

This boy, a congenital deaf mute, was seen to have a swelling of his forehead which had slowly developed over a period of one year. There was no history of trauma, and there had been no headache or pain associated with the tumour. There had been no visual disturbance or noteworthy upper respiratory infection.

On Examination (*Fig.* 588).—Immediately above the glabella there was a bony-hard swelling in the midline, measuring 1¾ × 2¾ in., and projecting ¾ in. from the surface. The overlying scalp was mobile and appeared normal. Olfaction was normal. There was no displacement or external paresis of either eye. Radiography of the skull showed an osteoma filling and expanding both frontal sinuses. The margins of the osteoma were poorly defined.

A B

Fig. 589.—*Case* 1. Post-operative photograph to show incision behind hair-line and cosmetic result. A, Frontal view; B, Lateral view.

At Operation.—A coronal incision behind the hair-line was made and a scalp-flap reflected forwards. A small right frontal bone-flap based on the temporalis muscle was made, the saw cuts anteriorly and medially being taken very close to the roof of the sinus. The anterior wall of the frontal sinus was paper thin in some parts and deficient in others. After excising the posterior wall of the sinus, the tumour, which occupied both frontal sinuses, was levered easily from its bed. No pus was seen. The tumour pedicle was close to the right fronto-nasal duct. The posterior wall of the frontal sinus was intact except for the operative defect. The dura was intact. As the anterior wall of the sinus had been destroyed by the tumour a tantalum plate was moulded and fixed into position over the cranial defect. The bone-flap was replaced and the scalp was closed with drainage for 24 hours.

The patient was given a course of systemic penicillin for ten days and convalescence was uneventful. The cosmetic result was satisfactory (*Fig.* 589).

The Specimen.—The osteoma (*Fig.* 590) was a perfect mould of the two frontal sinuses it had occupied and expanded; it weighed 53·9 g. Histological examination showed an ivory osteoma covered by ciliated epithelium.

SUBSEQUENT PROGRESS.—Six months later a tender fluctuant swelling appeared over the plate, but this subsided after a course of systemic penicillin. After a further four years there was a recurrent infection and the patient was re-admitted to hospital. Through the same incision the plate was exposed and found to be raised over

FIG. 590.—*Case* 1. Osteoma excised from frontal sinus. (× ⅔.)

dense fibrous and granulation tissue which had filled and obliterated the cranial defect. The plate was excised and the granulation was not disturbed. The wound healed well and three years later there had been no recurrence of inflammation and the cosmetic result remains satisfactory.

Group 2.—

Case 2.—G. L., female, aged 28. Fronto-ethmoidal osteoma invading right orbit, occasioning deformity, visual disturbance, and headaches.

This patient was transferred from the ophthalmological department with the history that for eighteen months the right eye had appeared to be less open than the left. During this period a painless, hard swelling had appeared immediately above the right eye, which had slowly increased in size. For the last seven months she had suffered from frontal headaches, worse in the mornings. The patient had long-standing myopia, but had developed diplopia just before admission to hospital. There had been no upper respiratory infection of note, and no nasal obstruction. There was no history of trauma.

ON EXAMINATION.—There was a partial right ptosis, and the right upper lid was displaced forwards 0·5 cm. by a bony hard swelling 1 cm. in diameter continuous superiorly with the superior orbital margin. The right eye was not displaced, but there was impairment of its upward movement resulting in vertical diplopia. The optic disks were normal and vision was 6/18 in the right eye and 6/12 in the left eye (corrected). Perimetry revealed no visual field defect. Olfaction was normal and there was no nasal obstruction. Radiography of the skull revealed an osteoma occupying the right frontal sinus, and extending into the right orbit and ethmoid cells.

AT OPERATION.—A coronal scalp-flap was reflected forwards, the incision being behind the hairline. A right frontal bone-flap, based on temporalis, was made. One saw cut was carried through the superior margin of the right frontal sinus, from which some pus escaped. *Staph. albus* was subsequently grown from this. The posterior wall of the sinus was excised to expose the tumour expanding it. An attempt was made to rock the osteoma from its bed, but as it was firmly embedded, piecemeal excision was undertaken. The tumour had filled the right ethmoidal air cells and had grown through the roof of the right orbit; the dura was intact. A total excision of the tumour was effected. After dusting the wound with sulphanilamide powder, the bone-flap was replaced, and the wound closed with drainage. Histological examination of the tumour revealed compact osteoma.

PROGRESS.—Convalescence was uneventful. As the anterior wall of the frontal sinus and the superior orbital margin remained intact there was no visible cranial defect. The bony swelling above the eye was no longer present, there was recovery from the ptosis and paresis of upward gaze of the right eye.

Case 3.—Mrs. E. J., female, aged 48. Fronto-ethmoidal osteoma invading right orbit and occasioning deformity, visual disturbance and pain.

Two years prior to admission to hospital this patient sustained two blows to the frontal region. The first injury was occasioned by a mangle handle springing back, and the second by walking into a street lamp. Shortly following the latter blow, she noticed a hard swelling of her forehead. At the same time she began to suffer from shooting pains behind the right eye, associated with transient visual disturbance, characterized by shimmering. For five months there had been a painless swelling on the right side of the bridge of the nose. There had been no upper respiratory infections of any note.

ON EXAMINATION.—A bony swelling was present in the midline and to the right of the glabella, 3 cm. in diameter, and raised 1 cm. The overlying scalp was healthy and mobile. The bridge of the nose appeared to be 'spread', and there was a small hard swelling just above the right inner canthus. Nasal breathing was free bilaterally and olfaction was normal. There was no proptosis or ptosis and the external ocular movements were full. The optic disks were normal and vision was 6/6 in both eyes. Radiography of the skull revealed a bony tumour expanding and filling the right frontal sinus and extending across the midline into the left frontal sinus.

AT OPERATION.—On Oct. 31, 1939, under general anæsthesia, a coronal scalp-flap was reflected forwards. A unilateral frontal bone-flap based on temporalis muscle was made. The posterior wall of the right frontal sinus was removed and there was no extension of the tumour into the cranial cavity. No pus or mucus was seen. The anterior wall of the sinus was greatly thinned and deficient in parts. The tumour occupied both frontal sinuses and had grown into the anterior ethmoidal cells on both sides, and into the right orbit. It appeared that the osteoma originated in the right frontal sinus, although no pedicle was demonstrated. It was removed piecemeal. The bone-flap was replaced and the wound closed without drainage, after applying 1-1000 acriflavine solution to the operative field. The tumour weighed 10·4 g. in all, and histological examination showed an compact osteoma.

PROGRESS.—Convalescence was uninterrupted. There was a small defect over the frontal sinuses where their anterior walls had been destroyed by the tumour.

The last two cases were admitted to hospital on account of intracranial infection.

Group 3.—

Case 4.—W. E., male, aged 60. Left fronto-ethmoidal osteoma invading left orbit and dura mater; occasioned proptosis, and subsequently orbital cellulitis and pneumococcal meningitis.

Following a blow from a stone in the frontal region at the age of 13, this patient developed bilateral retinal detachments resulting in loss of vision in both eyes. For six years prior to the present illness, there had been increasing proptosis of the left eye, thought to be due to an orbital osteoma. There had been no headache or pain associated with the condition. He was observed during this time and two weeks before admission

developed an acute upper respiratory infection. After nine days the proptosis suddenly increased and there was severe pain in this area accompanied by sickness. A fluctuant swelling appeared above the left eye from which thick pus was aspirated.

FIG. 591.—*Case* 4. Radiograph to show orbital and intracranial extension of a large fronto-ethmoidal osteoma.

ON EXAMINATION.—An extremely ill and delirious man. There was a pyrexia of 106° F. The left eye was displaced downwards and forwards and there was a red fluctuant swelling of the left upper lid. The cornea was ulcerated and the conjunctiva œdematous. The left fundus could not be examined. There was a total retinal detachment of the right eye and there was no perception to light in either eye. There was severe meningeal irritation, but there were no focal neurological signs. Radiographs of the skull revealed a large osteoma occupying the left frontal and ethmoidal sinuses, and extending into the left orbit (*Fig.* 591). Lumbar puncture revealed turbid fluid from which pneumococci were cultured. A diagnosis of orbital cellulitis and acute meningitis was made. The abscess over the left eye was drained; *Staph. aureus* was cultured from the pus. The infection responded to a course of intrathecal and systemic penicillin.

After five weeks the patient's condition had sufficiently improved to allow excision of the tumour.

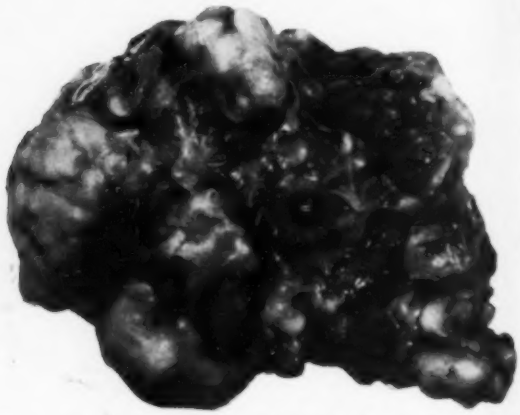


FIG. 592.—*Case* 4. Fronto-ethmoidal osteoma removed at operation. ($\times \frac{2}{3}$.)

AT OPERATION.—A left frontal bone-flap was turned down. The anterior wall of the frontal sinus was largely deficient. The dura was very adherent to the posterior wall of the sinus and to the roof of the orbit; as separation of the dura was difficult, the tumour was levered from its bed from in front. This bed extended into the right frontal sinus, the left orbital cavity, ethmoid cells, and the anterior cranial fossa, where the posterior wall of the frontal sinus had been eroded. The dura was greatly thinned and it had been destroyed in one part by the intracranial extension of the osteoma, thus providing the route for spread of infection from the nasal cavity to the subarachnoid space. No site of attachment of the osteoma to the wall of the sinus could be discovered. An intradural repair of the dural defect was effected with fascia lata, thus isolating the subarachnoid space from the

FIG. 593.—*Case* 5. Radiograph to show osteoma occupying left frontal sinus.

FIG. 594.—*Case* 5.—Lateral radiograph of skull showing osteoma expanding frontal sinus, and thorotrast in abscess cavity of left frontal lobe.

upper respiratory tract. The bone-flap was replaced, but there was a considerable cranial defect caused by destruction of the anterior wall of the left frontal sinus by the osteoma. The tumour measured 7 × 6 × 6 cm. (*Fig.* 592), and section showed it to be a mixed cancellous and ivory osteoma.

The patient made a good recovery and the wound healed well. The left eye had been destroyed by the infection; there were persisting granulations from the left upper lid and the left conjunctiva for four weeks, but ultimately the orbital infection subsided and the lids closed. The patient subsequently declined to have a cranioplasty performed.

Case 5.—C. G., male, aged 45. Left frontal osteoma, invading orbit; causing external deformity, and subsequently a cerebral abscess.

This patient had noticed a painless prominence in his left frontal region for twelve years; it was preceded by a closed head injury resulting in unconsciousness for three days. Five weeks before admission he had a mild upper respiratory infection for a few days, accompanied by low back pain. He was able to return to work for two days, but he then developed increasingly severe frontal and occipital headaches, worse in the mornings, and often accompanied by sickness. In the last week he had difficulty in remembering names and had become increasingly drowsy. There had been no previous visual disturbance.

On Examination.—A somnolent patient who was retarded and unable to concentrate. There was a severe expressive dysphasia. There was a prominence of the left frontal region of 0·5 cm., extending from the midline laterally for 4 cm. and from the superior orbital margin upwards for 3 cm. The left eye was not displaced. There were no signs of meningeal irritation and the patient was afebrile. There was low swelling of the left optic disk and the left pupil was larger and less reactive to light than the right. There was a right facial weakness and the grip of the right hand was impaired; the right cremasteric reflex was absent. Plain radiography of the skull (*Fig.* 593) revealed a large osteoma expanding the left frontal sinus. The blood leucocyte count was 13,000 per c.mm. and the erythrocyte sedimentation rate was 19 mm. in the first hour. It was believed that the left dilated pupil was evidence of a tentorial pressure cone and that immediate surgical intervention was indicated.

Fig. 595.—*Case* 5. Photograph of a section through the osteoma excised from the left frontal sinus. (× ⅔.)

Ventriculography performed on the day of admission revealed a left frontal space-occupying lesion. Through a left frontal burr opening, at a depth of 4 cm. a thin-walled abscess was entered and 22 c.c. of pus evacuated. 50,000 units of crystalline penicillin and 1·5 c.c. of thorotrast were instilled into the abscess cavity. There was an immediate improvement in the patient's level of consciousness. Culture of the pus yielded a pure growth of *H. influenzæ* sensitive to aureomycin, which the patient was then given systemically.

Fig. 596.—*Case* 5. Photograph taken one year after craniotomy, showing satisfactory cosmetic result.

Fig. 594 is a radiograph taken two weeks after the above procedure; it shows the osteoma in the frontal sinus, and the abscess cavity containing thorotrast.

Three and a half weeks following admission a left frontal craniotomy was performed. The posterior wall of the left frontal sinus was extremely thin and deficient at one point. The sinus mucosa was adherent to the dura here and this appeared to be the route for the intracranial spread of infection. After excising the posterior wall of the sinus the osteoma was removed whole with little difficulty; no definite site of attachment to the sinus could be determined. There were 2 c.c. of pus in the sinus. There was a large defect of the orbital roof, which had also been depressed. The mucosa of the sinus was stripped and removed. The dura was opened and a small frontal lobectomy performed to include the abscess. There were inflammatory changes and some thickening of the meninges where the sinus mucosa had been adherent to the dura. 100 mg. of streptomycin were

instilled into the wound and the dura closed. Gelatin sponge was used to cover the orbital roof and frontonasal duct, and the dura at the site of the route of entry of the infection. The anterior wall of the frontal sinus remained intact. The wound was then closed.

THE SPECIMEN.—The tumour weighed 12 g. and measured 6 × 2 × 2 cm. It was lobulated and surrounded by an adherent layer of periosteum. Section revealed a cancellous red centre surrounded by dense white bone (*Fig.* 595). Histological examination after decalcification showed partly a compact and partly a cancellous structure. The latter was composed of irregularly arranged trabeculæ in which areas of bone formation and destruction were seen. The medullary spaces between the trabeculæ were filled with loose fibrous tissue.

PROGRESS.—Convalescence was uninterrupted. The only residual neurological deficit was some difficulty in calculation. The left third nerve paresis disappeared. Although the low left frontal prominence remained, as there was no cranial defect the cosmetic result was satisfactory (*Fig.* 596).

TREATMENT

If neglected, osteomata arising from the paranasal sinuses may occasion headache, deformity, visual disturbance, upper respiratory infections, and, most dangerous of all, intracranial infection. Even attempts at excision were hazardous until the present century: Paget (1867) reported a case of an osteoma, presenting in the orbit, which was partially sawn off; the patient, however, died of meningitis post-operatively. Parsons (1904), in his description of orbital osteomata, almost certainly of paranasal sinus origin, noted that they might attain an enormous size, and that death from intracranial infection was common whether or not an attempt at surgical excision was made. Teed (1941), found the operative mortality to be over 3 per cent, even since the introduction of aseptic surgery.

In view of the complications to which they may give rise it is clear that these tumours should be excised early before they attain sufficient size to occasion these complications. Although this view has been fairly widely held in recent years, *Case* 4 was observed for six years, with a progressive deformity, until at length he developed acute meningitis. The method of excision has also varied, whether it be a transorbital approach for an osteoma presenting in the orbit, or a direct external approach to the frontal or ethmoidal sinuses.

Cushing (1927), however, reported 4 orbito-ethmoidal osteomata; he excised the tumour by means of a frontal craniotomy in 3 of them. The dura had been eroded by the tumour in each case: the first and second cases succumbed from subsequent intracranial infection, but the third and fourth survived, as this complication was avoided by repairing the dural defects with fascial grafts, and thus shutting off the intracranial contents from the upper respiratory tract. On account of the possibility of a dural defect existing, therefore, Hoover and Horrax (1935), reporting a case of an orbitofrontal osteoma, recommended that a frontal craniotomy be carried out, even if there had been no previous intracranial infection, so that an adequate repair to the dura could be made if indicated. Armitage (1931) reported a case complicated by pneumocephalus and cerebrospinal fluid rhinorrhœa; he covered the dural defect with a mucosal flap, but recurrences were only finally prevented by sealing the defect with a fascial graft.

Deformity is frequently caused by the tumour, and may be increased by its removal. If a direct approach is made through the anterior wall of the frontal sinus, unless the tumour contained within is very small, an unsightly bony defect must be unavoidable. To overcome this disadvantage Conley (1944) described the use of tantalum to cover the defect at the time of removal. This is not without danger, as infection from the sinus might spread to the tissue around the plate and there will be a risk of having to remove this at a later date, as happened in *Case* 1.

As an alternative method to prevent post-operative deformity Gibson and Walker (1952) described a technique whereby they reflected forwards a coronal scalp-flap, commencing behind the hairline and carried down to the orbital margins, with the anterior wall of the frontal sinus still attached to the scalp, replaceable after excision of the tumour. Although the procedure might be satisfactory in the presence of tumours confined to the frontal sinus, it is still open to the criticism of inadequate exposure should there be a dural defect; furthermore such a lesion could easily be overlooked. Howells and Jones (1954) were able to avoid a visible defect in some of the cases in a series described by them by entering the frontal sinus through its floor; this would also only be possible if the tumour were small.

As advocated by Lang and Armour (1919) and Hoover and Horrax (1935), a transfrontal or Naffziger approach will allow preservation of the anterior wall of the frontal sinus if this has not been destroyed by the tumour. *Cases* 1, 3, and 4, being relatively advanced, showed very thinned or deficient anterior walls to their frontal sinuses, and there was inevitably a cranial defect following excision of the tumour; had these patients come for treatment earlier, the defects might have been avoided.

A final reason for advocating the transfrontal approach to these tumours, also given by Lang and Armour (1919) and Hoover and Horrax (1935), is that in the event of their orbital extension this method will give the best means of access for their excision; a wide exposure of the orbital contents is relatively simple and there is little risk of damaging the eye or its adjacent structures.

The advisability of excision must be considered in each case. If a very small osteoma, found on routine radiological examination only, is not occasioning symptoms, then it may be safely left, providing the patient is kept under observation. When a tumour is occasioning symptoms, such as from obstruction of the frontonasal duct, providing it has not already completely filled or expanded its parent sinus, then its excision through an external approach may be satisfactory. If an osteoma is found to be obliterating its parent sinus it is possible that the dura has already been damaged. So it is in these cases, and those in which the tumour has spread even beyond the sinus, that prompt excision is indicated. Furthermore, a transfrontal approach will be the most satisfactory.

If the tumour is confined to one side then a unilateral bone-flap will suffice. If, however, it crossed the midline it might be more profitable to take out a frontal bone block after turning down a coronal scalp-flap, the incision for which is behind the hairline. The dura can readily be separated from the posterior wall of the frontal sinus, and the roofs of the orbit and ethmoidal air cells. As these walls are thin structures they are easily penetrated, and a good exposure of the tumour will be obtained. It is, as a rule, an easy matter to lever the latter from its bed, although on occasions piecemeal excision will be required. If the dura is thinned or deficient it can be repaired by a graft of pericranium or fascia lata. Unless the defect is very small, an intradural repair is preferable. The bone-flap is replaced, together with the bone chips in the burr openings, if there is no infection, and the scalp flap sutured back into position. Unless the anterior wall of the frontal sinus has been destroyed by the tumour there should be no visible bony defect. If this has occurred a cranioplasty can be carried out, preferably at a later date, in view of the risk of infection.

SUMMARY

Five cases of osteomata arising in the paranasal sinuses are reported. A review is given of the theories concerning their aetiology, pathology, and symptomatology. Emphasis is laid on the complications occasioned by their spread. It is believed that early excision is desirable, and in many cases this should be by a frontal craniotomy.

The cases recorded were under the care of Mr. J. E. A. O'Connell, who the author wishes to thank for permission to report them and for his help in the preparation of this paper. Thanks are also due to the Photographic Department of St. Bartholomew's Hospital for the photographic reproductions.

REFERENCES

ARMITAGE, G. (1931), *Brit. J. Surg.*, **18**, 565.
ARNOLD, J. (1873), *Virchows Arch.*, **57**, 145.
CONLEY, J. J. (1944), *Arch. Otolaryng., Chicago*, **40**, 295.
CUSHING, H. (1927), *Surg. Gynec. Obstet.*, **44**, 721.
DOLBEAU, M. (1871), *Mém. Acad. Méd.*, **30**, 1.
DOWLING, J. B. (1945), *Arch. Otolaryng., Chicago*, **41**, 99.
FETISOFF, A. G. (1929), *Ann. Otol., etc., St Louis*, **38**, 404.
GIBSON, T., and WALKER, F. M. (1952), *Brit. J. plast. Surg.*, **4**, 210.
GUNS, P. (1952), *Acta otc-laryng., Stockh.*, **42**, 359.
HALLBERG, O. E., and BEGLEY, J. W. (1950), *Arch. Otolaryng., Chicago*, **51**, 750.
HARRISON, W. J. (1942), *Amer. J. Ophthal.*, **25**, 1233.
HEWETT, Q. (1867), *St Geo. Hosp. Rep.*, **2**, 1.
HILTON, J. (1836), *Guy's Hosp. Rep.*, **1**, 493.
HOOVER, W. B., and HORRAX, G. (1935), *Surg. Gynec. Obstet.*, **61**, 821.
HOWELLS, G. H., and JONES, H. M. (1954), *J. Laryng.*, **68**, 177.
LANG, W., and ARMOUR, D. (1919), *Proc. R. Soc. Med.* (Sect. Ophth.), **12**, 16.
MALAN, E. (1938), *Arch. ital. Chir.*, **48**, 1.
PAGET, J. (1867), *Lectures on Surgical Pathology*. London: Longmans.
PARSONS, J. (1904), *Pathology of the Eye*, **2**, 745. London: Hodder and Stoughton.
TEED, R. W. (1941), *Arch. Otolaryng., Chicago*, **33**, 255.

A GIANT LEIOMYOMA OF THE KIDNEY

BY C. L. CLINTON-THOMAS, MALAYA

SMALL connective-tissue tumours of the kidney are not uncommon incidental findings in the post-mortem room.

Fibromas, myomas, and lipomas in that order of frequency occur as small circumscribed nodules, most often in the cortex. These have been well described by Newcomb (1936), who found 55 small subcapsular leiomyomatous nodules during 1172 necropsies. Despite the relatively frequent occurrence of these small connective-tissue tumours of the kidney, unlike the related neoplasm of the uterus, they seldom become clinically significant. Very occasionally, however, they grow sufficiently large to attract attention. This increase in size is not infrequently accompanied by sarcomatous change; indeed, as in other connective-tissue neoplasia, no sharp line of demarcation can be drawn between the benign and malignant mesodermal tumours of the kidney and, in reviewing the literature, it is necessary to consider renal leiomyoma and leiomyosarcoma together.

Patch (1937), reporting a case of malignant leiomyoma of the kidney treated by nephrectomy, reviewed the literature and could only find 7 other cases; those of Busse (1899), Ochsner (1899), Hoffman (1914), Bugbee (1929), Berry (1929), Crosbie and Pinkerton (1932), and Counseller and Menville (1936). The cases reported by Berry and by Crosbie and Pinkerton were considered malignant; the remainder benign. He overlooked cases of renal leiomyosarcomata reported by Cooke (1933), Swan (1933), and Smith (1935), and the case of renal leiomyoma reported by Kretschmer (1930). Mintz (1937) reported 4 cases of renal leiomyosarcomata from the Massachusetts General Hospital, including 1 case with bilateral lipoleiomyosarcomata.

Gordon, Kimmelstiel, and Cabell (1939) reported a case of leiomyoma of the kidney and reviewed the literature.

Weisel, Dockerty, and Priestley (1943) reviewed 35 cases of renal sarcoma treated at the Mayo Clinic from 1904 to 1940: these included 3 cases of leiomyosarcoma which histologically resembled a malignant uterine fibroid.

Shaheen, Cassano, and Lisa (1944) reported a symptomless leiomyosarcoma of the kidney found at post-mortem.

Tetelman and Lisa (1945) described another small renal leiomyosarcoma found incidentally at autopsy. Willis (1948) stated that he had examined two renal leiomyomata treated by nephrectomy, one weighing 43 oz. and the other 8 cm. in diameter.

Other cases of leiomyoma of the kidney have been reported by Heggie and Alstead (1936), Bailey and Harrison (1937), Lytle (1939), Crabtree (1944), Zuckerman, Kershner, Laytner, and Hirschl (1947), and Petkovic (1951).

Bagolan (1950) reported a case of bilateral renal leiomyosarcoma.

FIG. 597.—Front view of patient before operation.

FIG. 598.—Back view of patient before operation.

Kretschmer (1952), reporting a case of leiomyosarcoma of the kidney, reviewed the literature and found 14 other cases.

Owen (1953) reported a case of renal fibromyoma, but histologically the tumour showed some evidence of malignancy and should have been called a leiomyosarcoma.

Kerr (1954) reports an interesting case of renal leiomyosarcoma in a man of 45 who had undergone a gastrectomy for a histologically similar neoplasm of the stomach a year previously: the tumours were not considered to be related.

Of interest is the frequent finding at post-mortem of smooth-muscle tumours, either leiomyomata or lipoleiomyomata, in the kidneys of patients dying from tuberose sclerosis—a rare hereditary disorder of the growth of tissues affecting many parts of the body. The tumours are usually small and multiple and remain symptomless, but occasionally they enlarge and death may follow from malignant change or uræmia (Kirpicznik, 1910; Hyman, 1922; Feriz, 1930; Dawson, 1954).

It is probable that less than 50 of these rare renal tumours have been reported to date.

The case which is now reported appears to be unique on account of the size of the tumour.

CASE REPORT

A Malay male, aged 23, was admitted to hospital on April 5, 1954, complaining of abdominal swelling.

HISTORY.—He had first noticed a lump in the right hypochondrium three and a half years previously. This had gradually enlarged until it filled his whole abdomen. He had been unable to work as a rice cultivator for the last year as he could not stoop down. Eighteen months previously he had attended another hospital where he had been told that he had fluid in the abdomen. Paracenteses had been attempted at several points but without result. He had been so disappointed at the failure to relieve his condition that he did not seek further advice until he found he was getting severe respiratory embarrassment on lying down, and he was having difficulty in riding a bicycle! He had never had any abdominal pain. His appetite was good; he denied any bowel or urinary symptoms.

ON EXAMINATION.—The patient presented a most bizarre spectacle (*Fig.* 597). His abdomen was so distended that he was unable to stand without an extreme lordosis, and he preferred to squat. Apart from his abdomen, his general appearance was healthy. There was no œdema of the lower limbs. Temperature and pulse were normal. B.P. 100/70. Hb 85 per cent (Sahli), above average from the local population. Total R.B.C.s 4,500,000 per c.mm., total W.B.C.s 7500 per c.mm.

Palpation of the abdomen revealed an enormous smooth solid mass which almost completely filled it, and was distending the right loin (*Fig.* 598); above, it disappeared under the costal margin and there was gross splaying of the lower ribs on both sides; below, it went into the pelvis. The lower part of the mass could be felt by a finger in the rectum. A small area in the extreme left flank was resonant on percussion, and only here were bowel sounds audible. The circumference of the abdomen at the level of the umbilicus was 53 in.

Investigations.—Attempts to elucidate the nature and origin of the tumour were fruitless. Intravenous and retrograde pyelography were carried out but X rays would not penetrate the mass, and neither kidney was demonstrated. A similar failure followed a barium meal. A radiograph of the chest was normal apart from elevation of the diaphragm and crowding of the ribs.

Examination of a mid-stream specimen of urine showed no abnormality.

In view of the general well-being of the patient it was thought that the tumour was probably benign, or at least operable.

FIG. 599.—Tumour just before removal, showing renal pedicle.

A tentative diagnosis of retroperitoneal lipoma was made, and it was decided to explore the abdomen.

AT OPERATION.— On April 10, 1954 under pentothal-cyclopropane-oxygen anæsthesia (Dr. A. S. Gardiner) the abdomen was entered through a long right paramedian incision extending from the costal margin to the pubis. The tumour filled the whole peritoneal cavity and no viscera were visible at first. The intestines could be felt in the left flank.

After tilting the operating table to the right it was possible partially to deliver the tumour. It was then seen to be retroperitoneal and the ascending colon and cæcum were found passing over its inner quarter. These were mobilized after dividing the posterior parietal

FIG. 601.—The tumour after section. The artery forceps mark the extent of the flattened and elongated kidney.

peritoneum on their lateral aspect. During this procedure many small and moderate sized blood-vessels passing into the substance of the tumour required ligation. It was by this time apparent that the tumour was arising from the right paravertebral gutter and was well encapsulated. Its further mobilization was easily effected apart from the difficulty caused by its great weight.

It was finally possible to expose the renal pedicle and ureter and to demonstrate that the tumour was arising in the kidney (*Fig.* 599). The renal vein was normal in

FIG. 600.—Patient after operation.

appearance, and on palpation. The left kidney was present and appeared to be normal. The renal vessels and ureter were then ligated and divided and the tumour

FIG. 602.—The whole specimen with a probe inserted into the ureter.

was removed. The other abdominal viscera showed no abnormality: The para-aortic lymph-nodes were not enlarged and the liver showed no evidence of metastases. After removal of much surplus peritoneum the posterior

parietal peritoneum was reconstituted. The retroperitoneal space was drained through a stab wound in the flank and the abdomen closed in layers.

Two pints of blood were given during the operation and the pulse, respiration, and blood-pressure were almost unchanged at its conclusion.

POST-OPERATIVE PROGRESS.—This was uneventful apart from a mild chest infection which responded to penicillin. He had some difficulty in adjusting himself

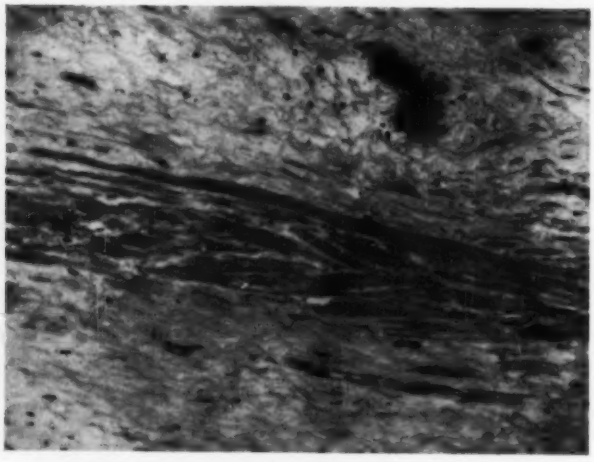


FIG. 603.—Low-power photomicrograph of the tumour. (× 90.)

to his new centre of gravity, but was finally discharged from hospital three weeks later. At this time he weighed 18 lb. more than his tumour. When last seen five months later he was extremely well. The abdominal muscles had almost entirely regained their former tone, but there was still much surplus skin and subcutaneous tissue (*Fig.* 600). He was advised cosmetic surgery but refused it.

PATHOLOGICAL REPORTS.—

1. *The Tumour.*—The tumour weighed 82 lb. (37,195 g.) and its shape is seen in *Figs.* 601, 602. It measured 23 × 18 × 8 in. (57·5 × 44 × 20 cm.) and was 65 in. (152·5 cm.) in circumference in its longest diameter. In the illustrations the flattened elongated remains of the kidney can be seen and a probe has been inserted into the ureter in the whole specimen. The tumour was pinky-yellow in colour with a firm well-defined capsule; small subcapsular hæmorrhages were scattered over the surface.

On section the tumour consisted of homogeneous pale greenish-yellow tissue with a faintly whorled appearance which was much more evident in the preserved state. The consistency of the fresh specimen was somewhat softer than a uterine fibroid.

2. *Histological Report* (Dr. A. H. Marsden).—Microscopically this gigantic tumour is composed mainly of loose collagen fibres, but in this fibrous tissue smooth muscle-fibres are scattered singly and in groups (*Fig.* 603). This is a leiomyoma, or fibromyoma—this description is preferred—of the kidney. The stretched atrophic kidney is still recognizable and the tumour appears to have arisen in the cortex, a few tubules still remaining between the tumour and the pelvis.

DISCUSSION

Lack of access to some of the relevant literature prevents a detailed analysis of the cases recorded, but certain conclusions can be drawn from the information which is available.

The origin of these tumours appears to be from the smooth muscle of the renal vessels, capsule or calices, and pelvis.

Patch (1937) quoted Dr. Rhea, the pathologist who reported on his specimen, as saying that with modern histological techniques many tumours previously labelled as fibroma or fibrosarcoma would probably be called leiomyoma or leiomyosarcoma to-day.

The great tendency for these tumours to undergo sarcomatous change or be malignant from their inception has already been pointed out; of the cases reviewed in this paper more than a half were malignant.

The case reported by Cooke (1933) is of special interest. At post-mortem a woman of 69, who had been known to have a renal tumour for five years and had refused operation, was found to have widespread peritoneal and hepatic metastases. On histological examination both the primary tumour and the metastases had the typical appearances of a benign leiomyoma.

It would appear that slow growth and the histological picture are in themselves insufficient data for labelling a given tumour as innocent, and a guarded prognosis should be made until a considerable time after nephrectomy has elapsed.

Willis (1948), who has repeatedly stressed this problem in connexion with mesenchymal tumours, noted that his specimens contained some rather cellular atypical areas which engendered caution in the prognosis.

No special sex incidence has been noticed. The cases recorded have been almost equally divided between men and women. Most of the cases have been in adults of the 20–40 age group. There is no record of a case in childhood and the maximum age was 85.

Symptomatology.—This in no way differs from that found in the more common renal carcinoma, except that distant metastases or their complications have not been recorded as the first manifestation of renal leiomyosarcoma.

The tumour may be symptomless, as in the case reported by Shaheen, Cassano, and Lisa (1944).

They have usually presented with one or more of the three cardinal symptoms or signs of renal growths—hæmaturia, pain, or palpable tumour.

Hæmaturia was the presenting feature in many of the cases of renal leiomyosarcoma. None of the tumours considered to be benign histologically caused hæmaturia, and it is evidently a sign of malignancy.

Pain was the presenting symptom in a considerable number of cases. It was usually a dull ache felt in the loin of the affected side, but in one case it was localized to the epigastrium and accompanied by vomiting.

Tumour. A palpable mass was present in many of the cases and was the presenting sign in a moderate number, as it was in the case which is the subject of this report.

Other less common symptoms were frequency of micturition, loss of weight, and vomiting.

Pyrexia as a significant clinical feature was not noted in any of the cases reviewed.

Diagnosis.—A pre-operative differentiation between the mesenchymal and epithelial neoplasms of the kidney is obviously quite impossible.

The diagnosis of a renal tumour is formed as a result of the usual investigations, or may not be possible if the tumour is very large, as in the present case, until laparotomy has been performed.

Treatment.—Nephrectomy by the lumbar or transperitoneal route is the only method of treatment which will be of benefit.

Experience has shown that leiomyosarcomata are insensitive to X-irradiation.

Prognosis.—Little information is available in the literature on the ultimate fate of patients with malignant myomatous tumours of the kidney who have undergone successful nephrectomy.

Cases alive and well after operation have been recorded by Berry (1929), Bugbee (1929), Crosbie and Pinkerton (1932), Swan (1933), Smith (1935), Patch (1937), Mintz (1937), Weisel, Dockerty, and Priestley (1943), Kretschmer (1952), and Kerr (1954).

OTHER LARGE BENIGN RENAL TUMOURS IN THE LITERATURE

The size and weight of the tumour in the case reported prompted a search of the literature for records of other giant benign renal tumours which have come to nephrectomy.

Gordon-Taylor (1930) reported successful nephrectomy for a fibro-adenoma of the kidney weighing 22 lb.; the tumour was described at the time as the largest benign renal neoplasm on record.

Nightingale and Lytle (1937), reporting a fibroma of the kidney, stated that Hektoen and Riesman (1901) in their *Textbook of Pathology* had described a renal fibroma weighing 37½ lb., and that Bruntzel (1882) reported a renal fibroma weighing 20 lb. The tumour in the case reported by Busse (1899) weighed 9 kilos and this author mentions a nephrectomy by Tillman for a fibromyxoma of the kidney which weighed 10 kilos.

Bailey and Harrison (1937) reported a benign adenoma weighing 3700 g. and a benign leiomyoma weighing 4940 g.

Tahara and Hess (1945) reported 2 cases of renal fibrolipoma, one weighing 1470 g., the other measuring 13·5 × 4·5 × 4·5 cm.

SUMMARY

1. A giant leiomyoma of the kidney is reported.
2. The literature is reviewed.
3. The operative treatment is described.
4. Other large benign renal tumours are briefly discussed.

I wish to express my thanks to: Mr. E. J. M. Weaver, for his assistance at the operation; Lieut. R. Whitaker, R.A.M.C., for the clinical photography; Dr. A. H. Marsden, of the Institute for Medical Research, Kuala Lumpur, for the pathological report; the Bland-Sutton Institute, Middlesex Hospital, for the photomicrograph; and the Director of Medical Services, Federation of Malaya, for his permission to publish this case.

REFERENCES

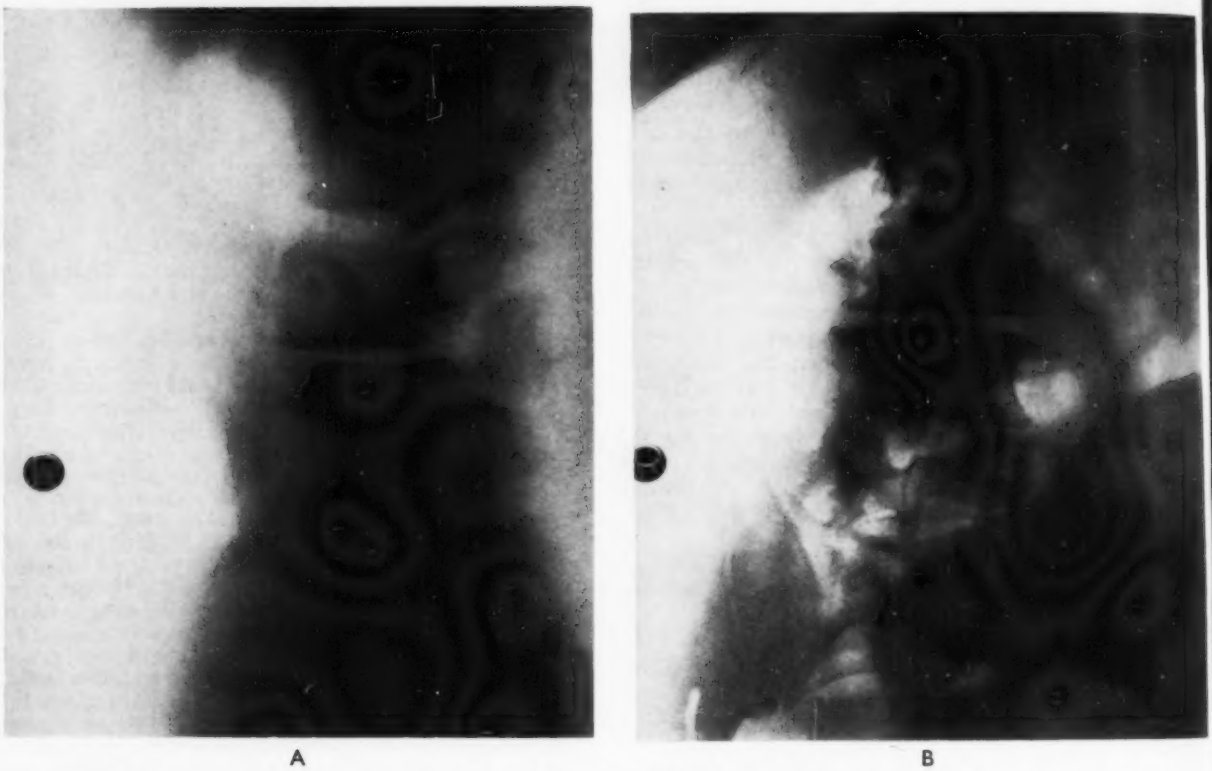
BAGOLAN, P. (1950), *Tumori*, **24**, 75.
BAILEY, O. T., and HARRISON, J. H. (1937), *J. Urol.*, **38**, 509.
BERRY, N. E. (1929), *Canad. med. Ass. J.*, **20**, 280.
BRUNTZEL, R. (1882), *Klin. Wschr.*, **19**, 745.
BUGBEE, H. G. (1929), *J. Urol.*, **21**, 363.
BUSSE, O. (1899), *Arch. klin. Med.*, **157**, 346.
COOKE, W. E. (1933), *J. Path. Bact.*, **37**, 157.
COUNSELLER, V. S., and MENVILLE, J. C. (1936), *J. Urol.*, **35**, 253.
CRABTREE, E. G. (1944), *J. Urol.*, **52**, 480.
CROSBIE, A. N., and PINKERTON, H. (1932), *Ibid.*, **27**, 27.
DAWSON, J. (1954), *Quart. J. Med.*, **90**, 113.
FERIZ, H. (1930), *Virchows Arch.*, **278**, 690.
GORDON, M. P., KIMMELSTIEL, P., and CABELL, C. L. (1939), *J. Urol.*, **42**, 507.
GORDON-TAYLOR, G. (1930), *Brit. J. Surg.*, **17**, 551.
HEGGIE, J. F., and ALSTEAD, S. (1936), *Glasg. med. J.*, **126**, 17.
HEKTOEN, L., and RIESMAN, D. (1901), *Textbook of Pathology*, **2**, 980. Philadelphia and London: W. B. Saunders Co.
HOFFMAN, E. (1914), *Beitr. klin. Chir.*, **89**, 250.
HYMAN, A. (1922), *J. Urol.*, **8**, 317.
KERR, J. A. (1954), *Brit. J. Surg.*, **41**, 478.
KIRPICZNIK, J. (1910), *Virchows Arch.*, **202**, 358.
KRETSCHMER, H. L. (1930), *J. Urol.*, **24**, 617.
— — (1952), *Ibid.*, **68**, 36.
LYTLE, S. N. (1939), *Med. Pr.*, **201**, 14.
MINTZ, E. R. (1937), *Ann. Surg.*, **105**, 521.
NEWCOMB, W. D. (1936), *Proc. R. Soc. Med.*, **30**, 113.
NIGHTINGALE, H. J., and LYTLE, S. N. (1937), *Brit. J. Surg.*, **25**, 57.
OCHSNER, E. H. (1899), *Chicago med. Rec.*, **16**, 395.
OWEN, R. A. C. (1953), *Brit. J. Surg.*, **40**, 403.
PATCH, E. D. (1937), *Brit. J. Urol.*, **9**, 345.
PETKOVIC, S. (1951), *Urol. cutan. Rev.*, **55**, 730.
SHAHEEN, A. L., CASSANO, C., and LISA, J. R. (1944), *J. Urol.*, **51**, 597.
SMITH, G. G. (1935), *Amer. J. Surg.*, **30**, 130.
SWAN, R. H. J. (1933), *Brit. med. J.*, **1**, 606.
TAHARA, C., and HESS, E. (1945), *J. Urol.*, **54**, 107.
TETELMAN, M. M., and LISA, J. R. (1945), *Ibid.*, **52**, 224.
WEISEL, W., DOCKERTY, M. B., and PRIESTLEY, J. T. (1943), *Ibid.*, **50**, 567.
WILLIS, R. A. (1948), *Pathology of Tumours*. London: Butterworth.
ZUCKERMAN, I. C., KERSHNER, D., LAYTNER, B. D., and HIRSCHL, D. (1947), *Ann. Surg.*, **126**, 220.

TUBERCULOSIS AT THE SITE OF SPONDYLOLISTHESIS

By A. H. C. RATLIFF

SENIOR ORTHOPÆDIC REGISTRAR, EDINBURGH ROYAL INFIRMARY (FORMERLY OF THE ROBERT JONES AND AGNES HUNT ORTHOPÆDIC HOSPITAL, OSWESTRY)

BOTH tuberculosis of the spine and spondylolisthesis are comparatively common, but the coincidence of these two conditions at the same level is extremely rare, and no account can be found in the English language. In the only relevant paper which can be traced, Nissen-Lie (1941), of Norway, describes 3 cases and discusses the possible correlation of these two disorders. No case, however, had radiological proof that a defect in the interarticular part of the lamina was present before the tuberculosis. The following case is, therefore, felt to be worthy of record.



A B

FIG. 604.—Radiograph, June 15, 1951, showing a well marked spondylolisthesis between the bodies of L.3 and L.4, with a narrowed disk space and a defect in the neural arch. A, Lateral view; B, Anteroposterior view.

CASE RECORD

A man aged 50, a bus driver, commenced with a dull mid-lumbar central backache in May, 1951. There was no injury, but the pain rapidly became severe. He could not move in bed, and was admitted to a local cottage hospital. X-ray examination at this time (*Fig.* 604) showed a well-marked spondylolisthesis between the bodies of L.3-4, a narrow disk space, and a defect in the interarticular part of the neural arch. A diagnosis of spondylolisthesis with a disk lesion was made, and he was put in a plaster jacket and discharged home. The backache gradually improved, the jacket was replaced by a Goldthwaite belt, and he returned to full work as a bus driver in March, 1952. He discarded his support at this time, and was completely symptom-free.

In June, 1952, lumbar backache recurred. He carried on work with increasing difficulty until January, 1953, but the pain became steadily worse; it was associated with feelings of stiffness and rather vague bilateral upper leg pains, especially in the morning. There was no clear history of root pain in the legs and the pain was not aggravated by coughing and sneezing. His general health now steadily deteriorated, with lassitude and slight loss of weight.

When admitted to hospital in May, 1953, he was a pale, ill-looking man. There were no chest symptoms or signs, and no family or contact history of tuberculosis. In the back there was a tender, mild mid-lumbar kyphosis localized to the L.4 level. Spinal movements were all grossly restricted by muscle spasm. No abdominal or loin abscesses were present, and there were no neurological signs in the legs: Lasègue's test was normal on each side. Radiography (*Fig.* 605) now showed a destructive lesion of the adjacent surfaces of the bodies of L.3 and L.4. The defect in the neural arch was more clearly visible.

INVESTIGATIONS.—E.S.R., 7 mm./hr. Hæmoglobin 14·8 g./100 ml. (100 per cent). Red-cell cytology normal. Wassermann, Kahn, and gonococcal complement fixation tests were negative. Radiography of the chest showed no abnormality.

TREATMENT by frame fixation, coupled with an open air régime, was instituted for six months. He was also given a three months' course of streptomycin (½ g. b.d.) along with para-amino-salicylic acid and isonicotinyl hydrazide. While on the frame his general condition showed a dramatic improvement, with return of appetite, increase in weight, and improvement in general appearance. At the end of this time the radiological appearances (*Fig.* 606) showed a remarkable improvement, with gradual obliteration of the tuberculous focus and recalcification of the adjacent bones. Mobilization was commenced in a short hip spica, and he was discharged home weight-bearing just before Christmas, 1953.

When last seen in June, 1954, he was very well and had resumed work wearing a Goldthwaite support.

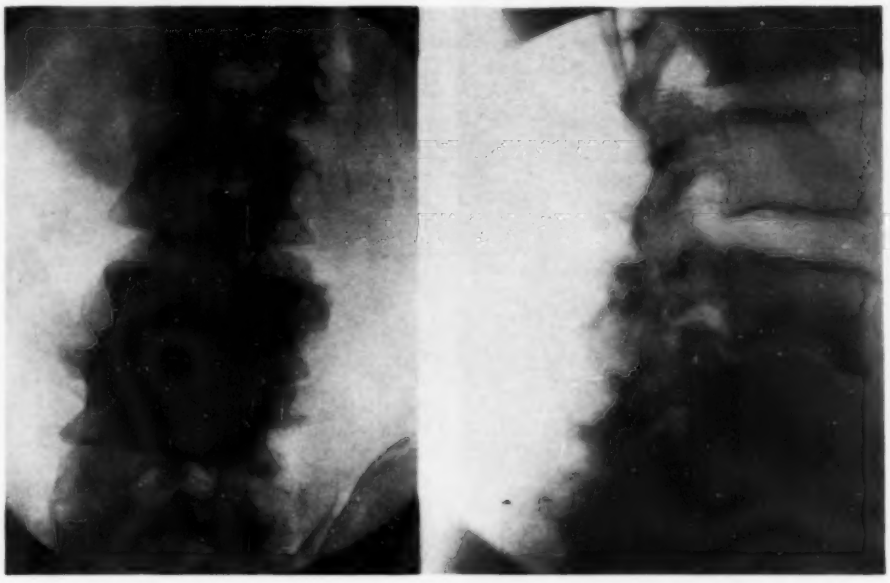


FIG. 605.—Radiograph, May 20, 1953, showing a destructive lesion between the bodies of L.3 and L.4 with an extremely irregular disk space and also the defect in the neural arch.

Radiographs (*Fig.* 607) showed progressive obliteration of the L.3–4 disk space, and it was felt that the two affected vertebral bodies will probably fuse spontaneously by bone.

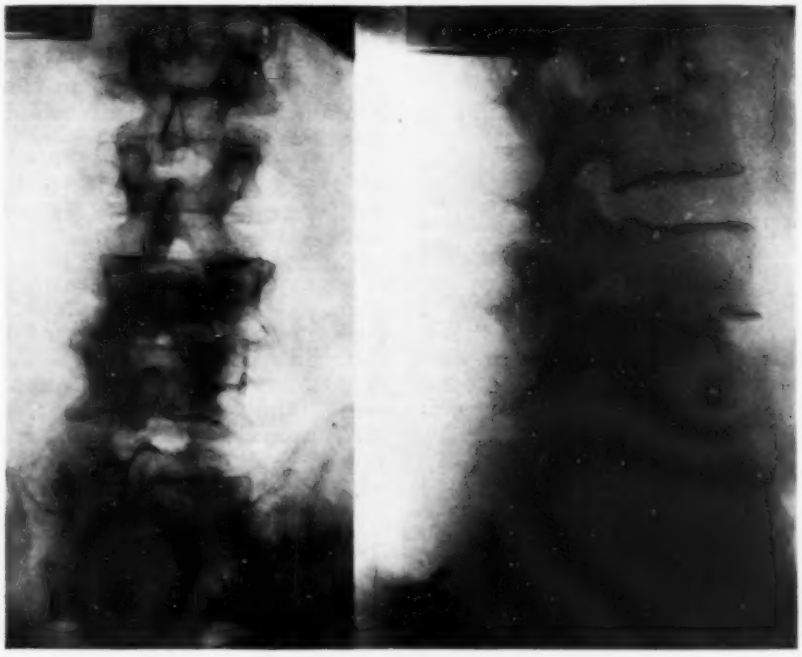


FIG. 606.—Radiograph, Jan. 19, 1954, at the end of a period of frame fixation, showing obliteration of the tuberculous focus and recalcification of the adjacent bones.

Comment.—Though there is no bacteriological or histological proof of tuberculosis in this case, nevertheless it is felt that the radiological appearances are sufficiently

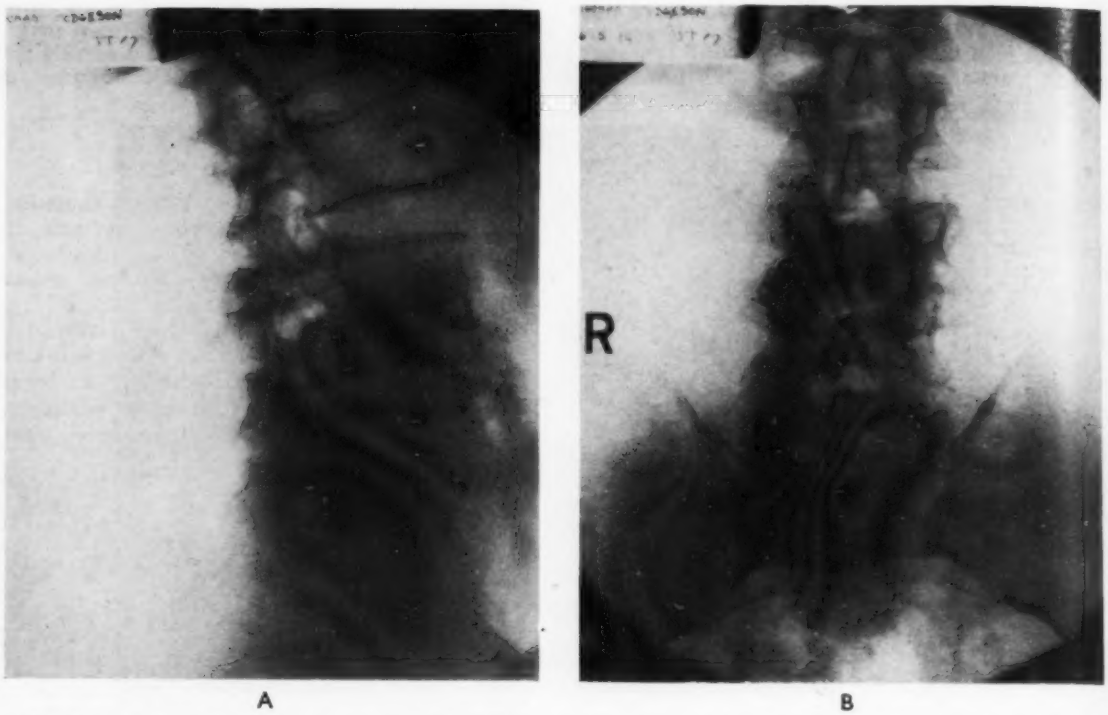


FIG. 607.—Radiograph, May 26, 1954, showing progressive obliteration of the L.3–4 disk space and commencing fusion between the affected vertebral bodies. A, Lateral view; B, Anteroposterior view.

characteristic to establish this diagnosis. The precise time of onset of the tuberculous process is debatable, and it may be that even in the first films of June, 1951, this disease had just commenced. There is, however, no doubt of a defect in the neural arch at this time, and therefore the tuberculous process arose at a site of spondylolisthesis.

DISCUSSION

Tuberculosis may produce forward slipping of one vertebral body on another :—

1. In the very rare instance where the destructive process involves and destroys part of the neural arch. Nystrom (1939) describes such a case in which it was seen during the operation that the whole arch was loose owing to tuberculous destruction.

2. Possibly, in extensive vertebral body destruction, by producing a 'stress lesion' of the neural arch (Nissen-Lie, 1941).

A case is reported here for the first time where there is proof that the spondylolisthesis was present before the tuberculous process, and therefore the above possibilities are eliminated.

SUMMARY

A case of spondylolisthesis and tuberculosis at the same site is reported in which a defect in the neural arch was present before the inflammatory lesion commenced.

I wish to thank Mr. H. Osmond-Clarke and Mr. William McKechnie for permission to publish this case.

REFERENCES

NISSEN-LIE, H. S. (1941), *Nord. med.*, **2**, 2431.
NYSTROM, GUNNAR (1939), *Acta chir. scand.*, **32**, 159.

RUPTURE OF THE ŒSOPHAGUS ASSOCIATED WITH LESIONS OF THE CENTRAL NERVOUS SYSTEM

By I. N. MACIVER, B. J. SMITH, B. E. TOMLINSON, and J. D. WHITBY

DEPARTMENTS OF NEUROSURGERY AND PATHOLOGY, NEWCASTLE GENERAL HOSPITAL, NEWCASTLE UPON TYNE

Rokitansky (1849), more than a century ago, recorded gastric and œsophageal lesions which were found in association with certain intracranial diseases. Cushing (1932) again drew attention to this association when he described cases of gastro-intestinal erosions, mucosal hæmorrhages, and perforation of the stomach, duodenum and œsophagus which accompanied severe intracranial lesions or followed intracranial operative procedures. Masten and Bunts (1934), and more recently Wyatt and Khoo (1949), French, Porter, von Amerongen, and Raney (1952), and Williams (1954), have added to the literature, and Kinsella, Morse, and Hertzog (1948) include "vomiting by a patient with a neurogenic lesion" as one of the recognized circumstances under which rupture of the œsophagus may occur. It is still, however, not generally recognized that rupture of the œsophagus is a complication liable to develop in patients with severe lesions of the central nervous system.

The present communication records the instances of œsophageal rupture found at autopsy in the Newcastle General Hospital during the three-year period November, 1951, to November, 1954. It describes the essential clinical and pathological findings in the cases associated with diseases of the central nervous system and the clinical features which should arouse suspicion of the intrathoracic catastrophe.

INCIDENCE

From 1951 to 1954, 1590 autopsies were performed and a ruptured œsophagus was found on 19 occasions. In 15 instances the rupture was associated with an intracranial lesion, in 2 with an acute disorder of the cervical spinal cord, in 1 with coma due to hepatic necrosis (severe infective hepatitis), and in 1 no other abnormality was found. In 452 of the total 1590 autopsies, intracranial disease was considered to be the major cause of death. Thus, in 452 instances of intracranial disease, a ruptured œsophagus was found 15 times; in 1138 'non-intracranial' cases rupture was found 4 times and in 2 of these a severe lesion of the cervical spinal cord was present. These figures alone appear to demonstrate conclusively that a relationship exists between certain lesions of the central nervous system and a rupture of the œsophagus.

LESIONS ASSOCIATED WITH RUPTURE OF THE ŒSOPHAGUS IN THIS SERIES

Table I records the type of central nervous system lesion with which the œsophageal rupture was associated, and summarizes other important data.

A skull fracture was present in 7 out of the 9 instances of head injury, an extradural hæmorrhage in 4, and extensive cerebral laceration in a further 4. In the traumatic cases there was no evidence of injury to any organ other than the brain. This is important, since it is known that rupture of the œsophagus may result from a severe blow to the abdomen or lower chest (Murdoch, 1928), and, clearly, road accidents are likely to produce such injuries. It seems unlikely, however, that rupture could result from such a blow without rib fracture, abdominal bruising, or visceral injury. Such findings were not present in any of our cases and, further, in 2 cases the trauma was known to be limited to the head (*Cases* 2, 11).

Of the 2 cases of cerebral tumour, 1 was a medulloblastoma of the fourth ventricle and the other was an astrocytic glioma of the right parietal lobe (*Cases* 5, 8). Both were operated on shortly before death. The spontaneous cerebral hæmorrhage was massive, disrupting the left internal capsule and also producing pontine hæmorrhages (*Case* 6). The 2 intracranial aneurysms (*Cases* 12, 17) acted initially as space-occupying lesions and neither produced subarachnoid hæmorrhage. Both were operated on shortly before death. The subdural abscess (*Case* 16) was secondary to suppurative frontal sinusitis and had been drained surgically on the day before death. Of the cervical cord lesions, one was an extensive softening of the cord following vascular thrombosis due to tuberculous osteitis with operative decompression of the cord three days before death (*Case* 9), and the other was a case of poliomyelitis with severe involvement of the cervical cord and lower medulla (*Case* 14).

In 3 of the above cases other lesions were found at post-mortem. In *Case* 1, although a traumatic incident producing coma initiated the illness, only three small areas of traumatic hæmorrhage were found in the left cerebral hemisphere at autopsy and severe chronic pyelonephritis was also present. In 1 of the cases of cerebral tumour (*Case* 8) multiple emboli were present in the right pulmonary vessels; the patient with poliomyelitis (*Case* 16) had severe bilateral bronchiectasis. In these instances, therefore, factors other than the intracranial damage may have contributed. With these exceptions the lesions were limited to the central nervous system and the thoracic cavity.

SYMPTOMS AND SIGNS

In most of these cases the discovery of a ruptured œsophagus at post-mortem was unexpected and the clinical findings were elicited from the case records, or by immediate inquiry from all medical or nursing staff who had contact with the patient. A few patients died shortly after admission to hospital, and in all a serious lesion of the central nervous system focused attention on the signs and symptoms of that lesion, so that information relevant to the chest conditions was sometimes inadequately recorded. In 3 instances (*Cases* 8, 13, and 17) a rupture was suspected in life but only proven at autopsy. In *Case* 8 the suspicion was aroused by pain in the right

Table I.—SUMMARY OF CASES

Case	Age and Sex	Presenting Features	Clinical Findings					
			Coma	Vomit	Pyrexia	Deterioration	Max. Pulse rate/min.	Max. R.R./min.
1	65 M.	Knocked down by car. Confused on admission. Increased drowsiness. On third day, spastic left arm. Blood-urea 230 mg. per cent. Died ninth day	+	+ once	104° F.	Indefinite	130	32
2	19 M.	Motor-cycle accident. Orbit penetrated by spike. Unconscious till death 48 hr. later in transit to N.G.H.	+	+	—	Indefinite	?	?
3	17 M.	Struck by cricket ball left temple. 1 hr. later copious vomiting followed by retching. 1 hr. later in deep coma. Died 24 hr. after operation	+	++ Brown fluid. Altered blood	103° F. axilla	Indefinite	144	36 during op. 8/min. on return to ward
4	28 M.	Struck by lorry. Compound fracture skull. Right hemiplegia. Rapid deterioration third day after operation and death within 24 hr.	+	++ Altered blood. Epistaxis	102° F.	Rapid	184	60
5	3½ F.	Vomiting and headache 7 weeks. Papilloedema. Ataxia. Sudden onset tachypnœa, stertor, and coma 10 hr. after operation. Died 5½ hr. later	+	—	99·2° F.	Sudden respiratory distress. Became unconscious	200+	36
6	38 M.	Known hypertensive. Sudden coma. Right hemiplegia. Deterioration with tachypnœa and tachycardia during last 12 hr. Died twelfth day	+	1	100° F. subnormal last 3 days	Rapid	144, iregular	55
7	7 M.	Fell from bicycle. Momentarily dazed. In deep coma 2¾ hr. later. No improvement after operation. Death 3 hr. later	+	—	?	Indefinite	140, irregular	64
8	60 M.	Blow on head. Dazed for 1 hr. Severe headaches followed and left hemiparesis developed after 10 days. Post-operative pain in right chest on day of operation with dyspnœa, fall of B.P. and death in 6 hr.	Terminal only	+	—	Sudden pain right chest. Dyspnœa. Cyanosis	Rapid. Irregular	? Dyspnœa
9	38 F.	Severe back pain 2½ years. Quadriplegia following anæsthesia dental extraction. Fourth day sudden pain left chest, breathlessness, and cyanosis. Died 18 hr. later	Terminal only	+ Little altered blood	105° F.	Rapid	136	48
10	5 M.	Knocked down by car. Unconscious, pale, shocked on admission. Left hemiparesis. Convulsions. Died 19 hr. after operation	+	—	100·8° F.	Slow	200	52
11	28 M.	Head injury in colliery. Just conscious on admission. Bleeding from ears. C.N.S. signs. 8 hr. later sudden coma followed by death in 1½ hr.	+	++ Altered blood. Epistaxis	?	Sudden coma	120	24 before coma. Periods apnœa after
12	56 M.	Seven years' history of headaches, failing vision, and mental deterioration. Drowsy on admission. Rapid deterioration of conscious level with rising pulse-rate 8 hr. after operation. Death 18 hr. later.	+	++ Dark brown fluid	?	Rapid 9 hr. after operation. Pulse climbing 4 hr. later	162	30

SUMMARY OF CASES

Chest Signs	Operation Anæsthetic	Central Nervous Lesion	Post-mortem Findings	Possibility of Survival
Bilateral basal crepitations last 48 hr.	Right parietal and occipital burr holes. Fourth day L.A.	Small bilateral subdural hæmorrhages over temporal lobes. Two small (1½ cm.) traumatic hæmorrhages right temporal lobe, one left temporal lobe	Lower 10 cm. œsophagus black and necrotic. Hæmorrhages both pleural; 20 oz. black fluid each pleural cavity. Necrosis posterior mediastinum. Chronic pyelonephritis. Stomach grossly dilated. Submucous hæmorrhages in cardia	Not expected
Nothing abnormal detected before transfer	Exploration and suture of orbital wound at local hospital L.A.	Compound fracture left orbital plate. Extensive laceration left frontal and parietal lobe with severe subarachnoid bleeding	Tear 1½ cm. long left lower œsophagus. Hæmorrhagic margins. Black, frothy fluid left pleural cavity. Numerous petechiæ left lung and pleura. Few submucous hæmorrhages at cardia of stomach	Not expected
Bilateral râles all areas	Exploration. Clot not found. G.A. Relaxant	Extradural hæmorrhage, left frontal lobe	5 cm. tear left lower œsophagus. 10 oz. blood-stained fluid left pleural cavity. Numerous subpleural petechiæ left lower lobe. Acute duodenal ulcer	Not expected
Dullness and diminished air entry right base	Elevation depressed fracture. G.A. Relaxant	Fracture left temporoparietal into base. Extensive laceration left temporal lobe and contusion right hemisphere	4 cm. tear left lower œsophagus. Collapse left lung. No pleural exudate recorded. Stomach and duodenum normal	Not expected
Patchy basal dullness right base. Bilateral basal crepitations	Exploration posterior fossa. Torkildson's operation. G.A. No relaxant	Medulloblastoma 4th ventricle. Internal hydrocephalus	Tear 3 cm. left lower œsophagus. 60 oz. blood-stained fluid left pleural cavity. Hæmorrhage into mediastinum and both lower lobes. 1½ oz. blood-stained fluid right pleural cavity. Stomach and duodenum normal	Yes
Bilateral râles and rhonchi all areas	Nil	Massive hæmorrhage into left internal capsule. Pontine hæmorrhage	2½ cm. tear right lower œsophagus. 8 oz. bile and blood-stained fluid right pleural cavity. Digestion right lower lobe. Fundus of stomach thin and friable	Not expected
Chest not examined after operation but said to be 'bubbly'	Evacuation extradural hæmorrhage 5 hr. after accident L.A.	Large clot left frontotemporal region into middle fossa. Clot 4 cm. thick	Hole 3 mm. across in left anterolateral œsophageal wall 2½ cm. from lower end. 10 oz. brown fluid left pleural cavity. Numerous petechial hæmorrhages over left lung. Severe mediastinal digestion. Hæmorrhages and erosions lower œsophagus. Stomach and duodenum normal	Yes
Diminished right basal air entry with crepitations and friction rub	Decompression. G.A. Relaxant	Large necrotic and hæmorrhagic astrocytoma right temporal parietooccipital lobes. No evidence of trauma	Tear 8 mm. long left anterior œsophagus. Surrounding œsophagus friable and hæmorrhagic. 20 oz. brown fluid left pleural cavity. Mediastinum œdematous, hæmorrhagic. Embolus right pulmonary artery. Stomach—chronic duodenal ulcer	Not expected
Dullness and diminished air entry left base. Bilateral râles	Laminectomy 4th–6th ribs. G.A. Relaxant	Severe spinal cord thrombosis	Longitudinal tear 4 cm. long left lower anterolateral œsophagus. 30 oz. thick brown fluid left pleural cavity. Numerous subpleural hæmorrhages. Tuberculous osteitis, dorsal spine. Stomach and duodenum normal	Yes
?	Exploration with removal of pulped brain. G.A. No relaxant	Compound fracture right temporal bone. Laceration right temporal lobe and corpus callosum	Linear rupture left lower œsophagus 3 cm. long. Little brown fluid left pleural cavity (2 oz.). Collapse left lower lobe. Stomach and duodenum normal	Doubtful
Nothing abnormal on admission. Not examined after collapse	Nil	Extensive fracture right frontal to occipital bones. Large right extradural hæmorrhage	Tear 1 cm. left lower œsophagus. 5 oz. dark, blood-stained, foul-smelling fluid left pleural cavity. Many subpleural hæmorrhages left lung and mediastinum. Stomach—several perforations over greater curvature	Not expected
Nothing abnormal before or 10 hours after operation	Right frontal and parietal burr holes. Ventriculography. L.A.	Enormous aneurysm left internal carotid bifurcation with hydrocephalus. Recent small pontine hæmorrhages	Linear tear 2½ cm. long right posterior œsophagus. 2 oz. blood-stained fluid both pleural cavities. Thick brown hæmorrhagic fluid posterior mediastinum. No perforation of pleura. Numerous subpleural petechial hæmorrhages both lower lobes. Stomach and duodenum normal	Not expected

Table I.—Summary of Cases

Case	Age and Sex	Presenting Features	Clinical Findings					
			Coma	Vomit	Pyrexia	Deterioration	Max. Pulse rate/min.	Max. R.R./min.
13	32 M.	Road accident; unconscious for ½ hr. Conscious on admission. Deteriorated third day—operation. Further deterioration 8 hr. post-operatively. Death 17 hr. after operation	+	++ Altered blood. Epistaxis	104° F.	Rapid	176	48
14	18 M.	Malaise 2 days. Then developed left hemiparesis and became restless and unco-operative. 2 hr. after admission coma deepened and developed stertor. Operation, but died 5 hr. later	+	+	104° F.	Rapid	150	26
15	55 M.	Knocked down by car. Unconscious for ½ hr. then regained consciousness. Sudden loss of consciousness next day. Admitted almost moribund. Cheyne-Stokes respirations. Died 9 hr. after admission	+	++ Altered blood. Epistaxis	102° F.	Sudden unconsciousness	Tachycardia post-op.	? Periods of apnœa. Cheyne-Stokes respirations
16	13 M.	Long-standing bronchiectasis. Weakness of legs, then ascending paralysis with involvement of thoracic muscles. Sudden collapse with hyperpyrexia and tachypnœa 4½ hr. before death	Drowsy	—	106° F.	Sudden collapse	150 ? 72 pre-op.	36
17	38 M.	Five months' history of temporal headaches with visual impairment. Aneurysm seen by angiography. 3 weeks later sudden coma with weakness left arm and face and neck rigidity. Operation performed 6 hr. later. Sudden regurgitation large quantity brown fluid. Death within 2 min.	+ Sudden	+ Large amount brown fluid immediately before death	101° F.	Sudden vomit, respiratory failure. Death 1–2 min.	136	26

chest, accompanied by dyspnœa and a fall in blood-pressure, but after autopsy the pain was attributed to a pulmonary embolism since the œsophagus had ruptured into the left pleural cavity. In *Case* 13 unexplained deterioration with hyperpyrexia and extremely rapid pulse and respirations raised the possibility of a rupture, but the dullness found at the left base cleared on postural drainage and suction and the patient died before further investigations were made. In *Case* 17 sudden regurgitation of a large quantity of brown fluid again suggested an œsophageal rupture, but the patient died within two minutes of this incident.

Spontaneous rupture of the œsophagus in an otherwise healthy person is characterized by vomiting, pain, shock, tachycardia, pyrexia, cyanosis, dyspnœa, surgical emphysema, pneumothorax, and pleural effusion. The following analysis shows the frequency with which these symptoms and signs were noted in our series.

Vomiting.—Thirteen cases were known to have vomited, 5 of them persistently; 2 died immediately after a copious vomit. In 7 the vomit was dark brown or resembled altered blood, but 4 had had epistaxis and 2 more had been intubated under general anæsthesia.

Pain.—Only 3 patients were conscious at the time of rupture and of these 2 complained of pain in the chest. In one it was on the side of the rupture and only of moderate severity. In the other it was present in the right upper chest and associated with a pulmonary embolism, whereas the œsophagus had ruptured into the left pleural cavity. The third, who was quadriplegic and very drowsy, collapsed suddenly without complaining of any pain. Fourteen patients were comatose and unable to complain of pain, although restlessness was reported in 6 of them.

Collapse.—Twelve cases showed a sudden or rapid deterioration of general physical condition, 4 deteriorated slowly, and 1 (*Case* 2) was dead on admission. In 7 it was associated with the onset or deepening of coma. There was a concomitant increase of pulse-rate in 12 and respiratory-rate in 10.

Tachycardia.—A tachycardia of over 100 beats per minute occurred in 16 cases, and in 7 it was over 150 per minute.

Pyrexia.—Eleven patients were pyrexial and, of these, 6 were hyperpyrexial.

Respiratory Signs.—

Tachypnœa.—Eleven patients had a marked tachypnœa of over 30 respirations per minute and 3 had a mild tachypnœa. In the remaining 3 cases there was inadequate information about this point. Bradypnœa occurred in 4 cases, once before and 3 times after the tachypnœa.

Dyspnœa.—The 3 conscious patients were dyspnœic from intercostal paresis or pulmonary infection apart from any effect due to the rupture.

SUMMARY OF CASES—*continued*

CHEST SIGNS	OPERATION ANÆSTHETIC	CENTRAL NERVOUS LESION	POST-MORTEM FINDINGS	POSSIBILITY OF SURVIVAL
Left basal dullness and diminished air entry which cleared on postural drainage and suction. Crepitations	Removal extradural clot right side. G.A. Relaxant	Right temporoparietal and basal fractures. Some extradural blood-clot still present at post-mortem	Air and 8 oz. dark blood-stained fluid left pleural cavity. 5 cm. longitudinal tear left lower œsophagus with marked necrosis surrounding œsophageal wall and mediastinum. Collapsed left lung. Numerous subpleural hæmorrhages left lower lobe and diaphragm. Stomach and duodenum normal	Doubtful
Extensive bilateral râles and crepitations	Drainage subdural abscess. G.A. Relaxant	Œdematous brain. Thin subdural layer of pus	Linear tear 1 cm. left lower œsophagus with surrounding necrosis for 3 cm. Blood and air in posterior mediastinum and beneath pleura. Hæmorrhages into diaphragm on both sides. Suppurative frontal sinusitis. Stomach and duodenum normal	Doubtful
Bilateral râles	Removal subdural clot through burr holes. L.A.	Right subdural and intracranial hæmorrhage. Fracture orbital plate	Tear 7½ cm. long left lower œsophagus. Blood-stained fluid left lower lobe. Numerous hæmorrhages left lung. Stomach and duodenum normal	Not expected
Dullness and diminished air entry left base which cleared with postural drainage and suction. Râles left upper and lower lobes	Nil	Poliomyelitis involving medulla severely	Tear left lower œsophagus for 2 cm., extending into cardia of stomach. 5 oz. blood-stained fluid left pleural cavity. Blood as high as upper posterior mediastinum. Blood in upper abdomen and numerous hæmorrhages into diaphragm	Not expected
?	Decompression and ligation internal carotid L.A. and Largactil	Aneurysm bifurcation right interna carotid with intracerebral rupture	Ragged tear lower œsophagus 3 cm. long. 9 oz. blood-stained fluid left pleural cavity. Air beneath pleura. Mediastinal digestion. Stomach and duodenum normal	Not expected

Physical Signs in the Chest.—The most common physical sign was the presence of râles or crepitations, which were recorded in 11 patients. Basal dullness was found in 5 cases, but in 2 it disappeared after suction and postural drainage and in another it was described as patchy. In four of these cases and in one other the breath-sounds were diminished at one base. Although the full classical picture of a pleural effusion was not seen, its presence should have, perhaps, been suspected at least once, judging by the presence of basal signs and the size of the effusion found at post-mortem (*Case* 9).

Pneumothorax and Emphysema.—The signs of a pneumothorax were not detected in any case and subcutaneous emphysema at the root of the neck was not seen during life or at post-mortem.

POST-MORTEM FINDINGS

In all 17 cases the rupture involved the lower third of the œsophagus, on the left side in 12, on the right in 2, and in 3 a large portion of the lower end was necrotic. In 13 of the 14 instances where the site could definitely be determined, the rupture was in the form of a linear tear, the long axis of which was in the line of the œsophagus. In one, a round hole 3 mm. across was present. The edges of the tear were usually ragged and the surrounding œsophagus œdematous and friable. Submucosal hæmorrhages were visible adjacent to the tear in 2 cases and in 1 case there was a number of mucosal erosions. In the remainder no macroscopical abnormality was seen, apart from the actual tear and its surroundings. The longest tear was 7½ cm., the shortest 3 mm., and all involved the lower 5 cm. of the œsophagus. In 5 cases fluid was present in both pleural cavities and in 11 on one side only (10 on left and one on right). In 1 case, although both lungs were collapsed, no record of fluid in the pleural cavities was made in the autopsy report.

Perforation of the mediastinal pleura had occurred in all but one. In this, although there was a blood-stained effusion in both cavities, the mediastinal pleura on each side was intact.

The quantity of fluid varied from 30 oz. in both pleural cavities to 2–3 oz. on one side only. In 9 the fluid was heavily blood-stained, in 5 turbid and brown, and in 2 frothy and black. On one occasion a blood-stained pericardial effusion was present.

The *p*H of the pleural fluid was estimated in 4 cases and was 6·3, 5·4, 4·6, and 4·2.

In all, some degree of lung collapse was present, and in 14, extensive subpleural hæmorrhages, principally over the mediastinal and diphragmatic surfaces of the lower lobe, were seen. In 10 cases hæmorrhage and œdema were present throughout the posterior mediastinum, occasionally extending as high as the bifurcation of the trachea, and extensive hæmorrhages into the diaphragm were recorded four

times. Air in the mediastinum and beneath the pleura was seen in 3 cases.

In all, some digestion of mediastinal structures and lung had occurred, varying from blackening of the pleura to extensive destruction of the mediastinum with superficial digestion of small areas of the lungs and diaphragm. In 2 cases this digestion exposed the nerves and blood-vessels of the mediastinum. In 7 cases lesions were present in the stomach or duodenum in addition. One œsophageal tear extended into the fundus of the stomach; in another several separate small perforations were present on the greater curvature; in a third, the fundus was extremely thin and friable, though actual perforation had not occurred; in two instances submucosal hæmorrhages were present in the cardia, a chronic duodenal ulcer was found in another, and in one an acute ulcer. In the other 10, no lesion was seen in the stomach or duodenum.

Histology.—Histological examination has shown that in most cases the disintegration of tissue around the actual tear is so severe that it is impossible to be certain of the state of the œsophagus before rupture. However, in the œsophageal wall adjacent to this, the tissues are usually normal; in 3 cases there was severe submucosal congestion with small hæmorrhages into muscle and submucosa. In one further instance a large hæmorrhage involved almost the entire thickness of the muscle wall. On 3 occasions a polymorphic infiltration of the tissues at the margin of the rupture was seen, and in 2 of these an inflammatory exudate was present around the entire circumference of the œsophagus at the level of the rupture. In a few cases preservation of the muscle wall was good right up to the edge of the tear, and in these no evidence of any pre-existing abnormality was seen. Examination of the lungs, diaphragm, and mediastinal tissues confirmed the presence of hæmorrhages and superficial digestion, and in one case there was an acute inflammatory exudate over the pleura.

DISCUSSION

The frequency with which a ruptured œsophagus has been found in the past three years has compelled us to consider the possibility that it is a post-mortem occurrence in some instances. We feel, however, that the evidence for regarding it as ante-mortem is overwhelming.

The shape of the lesion is inexplicable as a post-mortem feature. The œsophagus could only rupture after death as a result of gross autolysis, and it is impossible for this to take the form of a linear tear. Furthermore, the position and shape of the lesion is identical with that found in spontaneous rupture (Barrett, 1946; Grigsby, Brown, and Cave, 1953; Collis, Humphreys, and Bond, 1944; Ware and Strieder, 1949; and Walker, 1914).

In almost all our cases evidence of ante-mortem reaction was shown by hæmorrhages beneath the pleura, in the posterior mediastinum, and the diaphragm. The findings in the chest have been identical with those reported in numerous publications on spontaneous rupture in which the ante-mortem nature of the lesion was never doubted; further, Williams and Boyd (1926) produced experimental evidence for stating that the disintegration of the œsophagus cannot be explained as a result of post-mortem digestion.

Lastly, if this were a post-mortem occurrence we would expect to find it accompanying many other diseases, whereas in this series it is almost entirely associated with acute lesions of the central nervous system. It is very difficult to decide whether œsophageal perforation results from acute erosion or from tearing of its wall as in spontaneous cases. Digestion often precludes any dogmatic statement about the previous condition of the œsophagus, but in the majority of cases the lesion is a longitudinal slit, as was found in many of the reported cases even though the authors consider the cause to be acute erosion. Presumably erosion would produce a circular deficiency in the œsophageal wall and not a slit. We do not consider loss of mucosa and superficial inflammatory cell infiltration in the lower œsophagus significant evidence that ulceration is responsible for the rupture. Post-operative acute œsophagitis is a well-recognized syndrom (Bartels, 1935; Pringle, Stewart, and Teacher, 1921; Olsen, 1948), and such a lesion in a torn œsophagus does not necessarily incriminate the inflammation as the exciting factor.

Erosions or hæmorrhages in the stomach and duodenum do not necessarily mean that the œsophageal tear is of the same type, and perhaps in some cases these gastroduodenal lesions merely cause severe vomiting, resulting in spontaneous œsophageal rupture. It is not disputed that œsophageal hæmorrhages and ulceration may play an important, and sometimes paramount role in producing the perforation, but the evidence that it is always or commonly so, is not convincing.

From the literature it is generally agreed that these gastro-intestinal lesions are related to the intracranial lesion rather than to some other common factor such as shock, though Penner and Bernheim (1939) consider this the fundamental cause. Since Cushing's paper (1932) many experiments have supported the concept that hypothalamic injury is responsible, though it is not agreed whether sympathetic or parasympathetic stimulation or paralysis plays the greater part.

French and others (1952) state that in 50 per cent of reported cases of gastro-intestinal lesions accompanying central nervous disorders the hypothalamus was involved, and in most of the others either the centripetal communications from the frontal lobe or centrifugal pathways from brain-stem or medulla were interrupted.

In this series the hypothalamus was directly involved in one case only (*Case* 12), and although many others showed multiple injuries, the main lesion probably interfered with centripetal communications from the frontal lobe by direct trauma or compression on the medial autonomic tracts and the wall of the third ventricle in 13. Of these, 6 involved the frontal lobe, 3 by hæmorrhage, and the others by trauma, extradural bleeding, and subdural abscess. The remaining 7 cases showed extradural hæmorrhage over the frontal-parietal area in 3 instances, trauma to the temporo-parietal region in a further 2, and finally hæmorrhage into a temporal lobe and a tumour of the anterior parietal area.

In the remaining 3 cases—namely, a tumour of the fourth ventricle, polio-encephalitis involving the medulla, and a spinal-cord thrombosis, centrifugal pathways from the brain-stem or medulla may have been involved.

Although the exact mechanism of œsophageal rupture is not known, it has usually been considered to follow upon erosion or acute ulceration.

From the evidence in this series we feel that a mechanical tear of the œsophageal wall usually causes the rupture, whether the wall is normal or already diseased by erosion or ulceration. This tear could occur during violent vomiting or retching, particularly in the presence of muscular incoordination produced by direct involvement of the hypothalamus or interference with the pathways to it.

In the majority the cerebral lesion was severe and in 8 cases recovery from this appeared impossible. Three patients, however, in this series (*Cases* 5, 7, and 9) were making good recoveries from the original nervous injury and on both clinical and pathological grounds their death at the time it occurred should be attributed to the chest complication. The remaining 6 cases were from a group which were capable of surviving but in whom the lesion of the central nervous system could have caused death. In these the œsophageal rupture should at least be regarded as hastening the end.

On the post-mortem evidence we have found great difficulty in assessing the time of the rupture in relation to death. In the cases where only a scanty amount of fluid in the pleural cavity was present, it seems justifiable to assume that the rupture occured close to death. On the other hand, the extensive destruction of the mediastinum and lungs in some cases appears to favour a considerable interval between rupture and death, although the continuance of digestion after death makes this a debatable point. In non-comatose cases of rupture the clinical features usually indicate the time of the rupture and would seem to be a much more reliable indication than assessment of post-mortem findings. This was so in the one instance of spontaneous rupture seen in the last three years.

Untreated, spontaneous rupture of the œsophagus is usually fatal in 1–3 days in patients who are otherwise well at the time of the catastrophe. From the post-mortem and clinical features in this series, it seems unlikely that any patient survived for longer than 24 hours after rupture of the œsophagus and a few possibly succumbed within an hour or even less.

This decreased survival period is to be expected, for all these cases were seriously ill, and unlikely to withstand any severe complication; in the comatose patient with severe cerebral or cervical cord damage the chest complication could well cause very rapid or even instantaneous death. This would appear particularly likely if a greatly raised intracranial pressure is present, for the reduced respiratory exchange caused by the chest complication could quickly prove fatal with an already severely embarrassed medulla.

Diagnosis is difficult because of the associated intracranial lesion, and the rapidity with which death may ensue in these seriously ill patients. Cushing's 2 cases (Cushing, 1932) deteriorated without neurological cause, developed hyperpyrexia and vomited 'coffee ground' material. One had 'moist sounds' in the chest. Fincher and Swanson (1949) described the clinical picture in their 3 cases as one of vomiting, followed by restless irritability, dyspnœa, cyanosis, hyperpyrexia, sweating, and deepening coma. In all 3 the vomit contained either bright red or altered blood at some time. In this series the clinical picture has been less well defined. The common finding was rapid deterioration associated with a rising pulse and respiratory rate in a comatose patient who was pyrexial, had 'moist sounds' in the chest, and who had been vomiting. The tachycardia was difficult to dissociate from the intracranial lesion, the effects of operation, and the pyrexia; the tachypnœa from the intracranial lesion, and pulmonary œdema, infection, or collapse.

Restlessness may be due to headache and will be absent if the coma is deep. It is, therefore, only when signs occur without any obvious intracranial cause that they become significant. The vomiting of altered blood is common after epistaxis and may occur with gastric lesions as well as œsophageal. A pleural effusion may not develop for several hours after a rupture (Scholefield, 1949) and a small effusion is difficult to detect in a comatose patient who is restless or resistent, and only 7 cases had 10 oz. or more of fluid in the pleural cavity at post-mortem, and in one both sides of the chest were equally involved. The signs of pneumothorax or subcutaneous emphysema, which would be equally diagnostic in the absence of direct injury to the chest, have not proved of any assistance so far. We feel that the possibility of a rupture of the œsophagus should be considered in any comatose neurosurgical patient with an unexplained deterioration associated with an increasing tachycardia and tachypnœa. Blood-stained vomit, pyrexia or hyperpyrexia, restlessness, râles or crepitations in the chest or basal dullness should increase the suspicion. All suspicious cases should have a radiograph of the chest in the hope of demonstrating mediastinal emphysema, a pneumothorax, or a pleural effusion. Radio-opaque oil may be injected down a Levin tube at the same time.

If clinical or radiological signs of a pneumothorax or pleural effusion are found, the aspiration of air or a little blood-stained or blackish fluid from the chest would be diagnostic.

Investigation will often prove negative, and in many cases death from the neurological lesion is inevitable; in some death may occur within a few minutes of the rupture; occasionally an associated abdominal perforation will be present. In spite of this a ruptured œsophagus of neurogenic origin has been successfully sutured by Dr. Abbott in America (Fincher and Swanson, 1949) and, if neurosurgical units realize the relative frequency of this condition, it is possible that an occasional life may be saved by prompt surgical intervention.

SUMMARY

Nineteen cases of ruptured œsophagus were found at post-mortem over a 3-year period, and, of these, 17 were associated with lesions of the central nervous system.

The symptoms, signs, and pathological findings in these 17 cases are described.

It is suggested that the rupture results from a mechanical tear in most instances, rather than from erosion or ulceration.

The relationship between lesions of the central nervous system and œsophageal rupture is briefly discussed.

Diagnosis of a ruptured œsophagus in a patient with a severe lesion of the central nervous system is extremely difficult, but certain clinical features are suggested which warrant an immediate investigation into the possibility of this complication. Prompt surgical intervention may occasionally be successful.

We wish to thank Mr. G. F. Rowbotham, Mr. L. P. Lassman, and Dr. G. Davison for permission to report their cases.

REFERENCES

BARRETT, N. R. (1946), *Thorax*, **1**, 48.
BARTELS, E. C. (1935), *Arch. Path.* (*Lab. Med.*), **20**, 369.
COLLIS, J. L., HUMPHREYS, D. R., and BOND, W. H. (1944), *Lancet*, **2**, 179.
CUSHING, H. (1932), *Surg. Gynec. Obstet.*, **55**, 1.
FINCHER, E. F., and SWANSON, H. S. (1949), *Ann. Surg.* **129**, 619.
FRENCH, J. D., PORTER, R. W., VON AMERONGEN, F. K. and RANEY, R. B. (1952), *Surgery*, **32**, 395.
GRIGSBY, M. E., BROWN, R. K., and CAVE, S. (1953) *Gastroenterology*, **25**, 398.
KINSELLA, T. J., MORSE, R. W., and HERTZOG, J. (1948) *J. thorac. Surg.*, **17**, 613.
MASTEN, M. G., and BUNTS, R. C. (1934), *Arch. intern. Med.*, **54**, 916.
MURDOCH, J. R. (1928), *Lancet*, **2**, 1292.
OLSEN, A. M. (1948), *Surg. Gynec. Obstet.*, **86**, 372
PENNER, A., and BERNHEIM, A. (1939), *Arch. Path.* (*Lab. Med.*), **28**, 129.
PRINGLE, J. H., STEWART, L. T., and TEACHER, J. H. (1921), *J. Path. Bact.*, **24**, 296.
ROKITANSKY, C. (1849), *A Manual of Pathological Anatomy*, **2**, 39. London: The Sydenham Society.
SCHOLEFIELD, J. (1949), *Brit. med. J.*, **1**, 348.
WALKER, I. J. (1914), *J. Amer. med. Ass.*, **62**, 1952.
WARE, P. F., and STRIEDER, J. W. (1949), *Dis. Chest*, **16**, 49.
WILLIAMS, R. D. B. (1954), *J. Pediat.*, **45**, 575.
WILLIAMS, T. H., and BOYD, W. (1926), *Surg. Gynec. Obstet.*, **42**, 57.
WYATT, J. P., and KHOO, P. N. (1949), *Arch. Path.* (*Lab. Med.*), **47**, 110.

ADENOMATOID TUMOUR OF EPIDIDYMIS

BY HUGH W. MACINTYRE

SENIOR REGISTRAR IN PATHOLOGY, WITHINGTON HOSPITAL, MANCHESTER

ADENOMATOID tumours of the epididymis are not common. The first case was described by Sakaguchi in 1916, and was called an adenomyoma. Since then additional contributions have been made, and a review of the literature was made by Longo, McDonald, and Thompson in 1951; they concluded that 71 authentic cases had been reported up to then.

In view of the rarity of the condition, the following case is described.

CASE REPORT

The patient, a male aged 40 years, gave a six-months' history of painless enlargement in the right side of the scrotum. The swelling, which was excised, was found to be attached to the lower pole of the right epididymis.

PATHOLOGY.—The specimen measured 2·0 × 1·5 × 1·0 cm. It was pale grey in colour, and had a thin fibrous outer covering; it was firm and rubbery in consistency, and had a somewhat whorled appearance. Grossly, it resembled a fibroma.

Histological examination showed, basically, two rather distinct fields. In one area there was a fibrous stroma in which were scattered small spaces lined by flattened endothelial-like cells, and which suggested lymph spaces (*Figs.* 608, 609), while the remaining parts were composed of glandular acini lined by low columnar cells (*Fig.* 610). Mucicarmine stain was negative. Mitotic figures were not seen. A number of foci of lymphocytes were present in the fibrous stroma, and towards the periphery were occasional smooth muscle strands.

DISCUSSION

The most common tumour at this site is the adenomatoid tumour. According to Longo, McDonald, and Thompson (1951), 74 per cent of primary neoplasms of the epididymis are benign, and the adenomatoid tumour accounts for 53 per cent of the entire group. Leiomyoma is the second commonest benign tumour. Of the malignant neoplasms, sarcoma is more common than carcinoma.

The adenomatoid tumour is relatively small, and does not, as a rule, exceed 2·5 cm. in diameter. The largest on record was reported by Hinman and Gibson (1924), and measured 9·0 cm. × 5 cm. It usually arises from the globus minor, and is more commonly seen on the left epididymis than on the right. Masson, Riopelle, and Simard (1942) were the first to recognize that adenomatoid tumours are found not only arising from the epididymis, but may also occur in the spermatic cord, as well as in the ovary, Fallopian tube, and uterus. They postulated the formation of a mesothelial anlage on the basis of certain cell characteristics.

Because the tumours are adjacent to the peritoneal lining, Evans (1943) also favoured the theory of mesothelial origin—and these authors called the tumour a 'mesothelioma'.

The tumour has also been considered to have an endothelial origin, because of the apparent similarity of the lining cells to those of the endothelium.

Some earlier reports had favoured an epithelial origin. Ewing indicated such a pathogenesis, and a diagnosis of adenocarcinoma was made in the case reported by Hinman and Gibson (1924). Other writers, Blumer and Edwards (1941), and Gordon-Taylor and Ommaney-Davis (1941), have called these neoplasms adenomas, on the grounds that the cell of origin was of epithelial nature.

Because of lack of proof of such an epithelial origin, Golden and Ash (1945) proposed the term 'adenomatoid', this designation being, they say, "morphologically correct and genetically neutral".

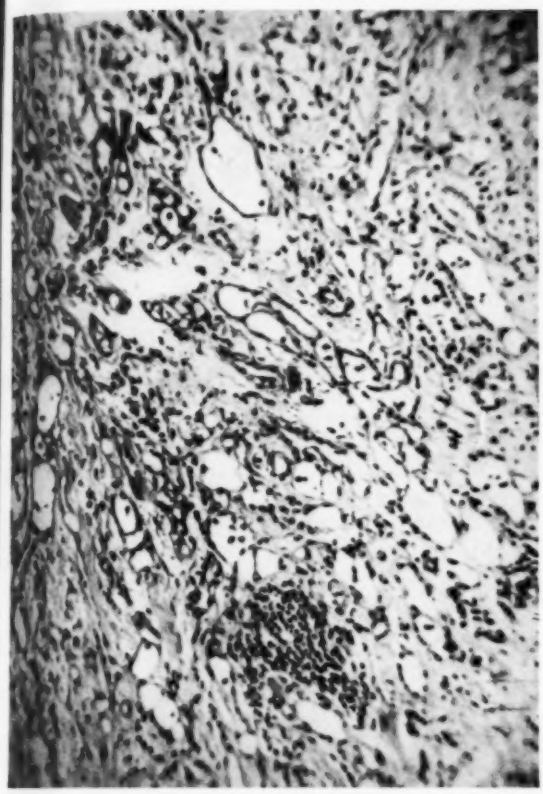


FIG. 608.—Showing small spaces lined by flattened endothelial-like cells. A focus of lymphocytes is present in the stroma. Hæmatoxylin and eosin. (× 80.)

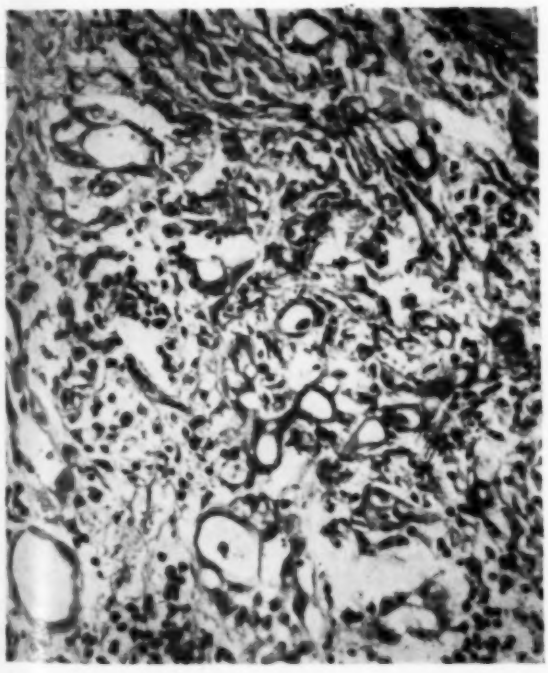


FIG. 610.—The glandular acini are lined by low columnar cells. Hæmatoxylin and eosin. (× 150.)

More recently, Longo, McDonald, and Thompson (1951) postulated a mesonephric origin, since the lesion is found only along the route of the mesonephros. This theory is supported by Teilum (1954), who considers that mesonephric tumours frequently may arise from a primitive mesonephric

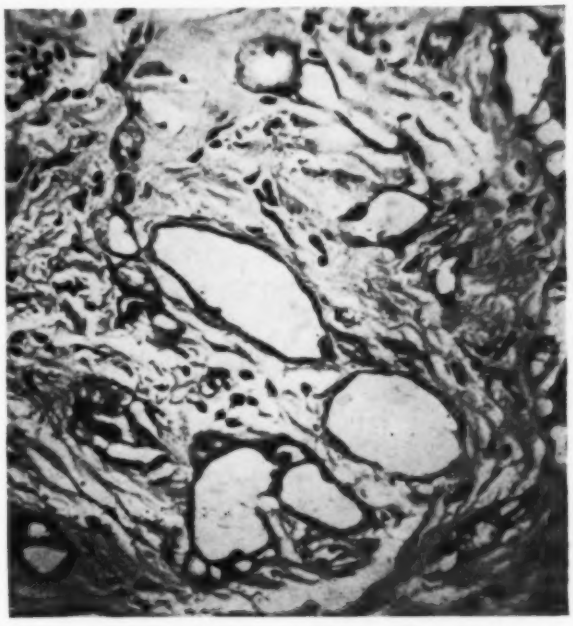


FIG. 609.—High-power view of *Fig.* 608. Hæmatoxylin and eosin. (× 225.)

mesoderm in the neighbourhood of the mesonephros and its ducts rather than in persistent epithelial remnants.

SUMMARY

An adenomatoid tumour of the epididymis is presented.

I wish to express my thanks to Dr. L. Stent for her advice and valuable criticism; and to Mr. S. S. Rose for permission to publish this case. I would also like to thank Miss Gibbon for preparing the photomicrographs.

REFERENCES

BLUMER, C. E. M., and EDWARDS, J. L. (1941), *Brit. J. Surg.*, **29**, 263.
EVANS, N. (1943), *Amer. J. Path.*, **19**, 461.
GOLDEN, A., and ASH, J. E. (1945), *Ibid.*, **21**, 63.
GORDON-TAYLOR, G., and OMMANEY-DAVIS, C. (1941), *Brit. J. Surg.*, **29**, 260.
HINMAN, F., and GIBSON, T. E. (1924), *Arch. Surg., Chicago*, **8**, 100.
LONGO, V. J., MCDONALD, J. R., and THOMPSON, G. J. (1951), *J. Amer. med. Ass.*, **147**, 937.
MASSON, P., RIOPELLE, J. L., and SIMARD, L. C. (1942), *Rev. canad. Biol.*, **1**, 720.
SAKAGUCHI, Y. (1916), *Frankfurt. Z. Path.*, **18**, 379.
TEILUM, G. (1954), *Acta path. microbiol. scand.*, **34**, 431.

SURGICAL TREATMENT OF TUMOURS OF THE HEART

A REPORT OF TWO CASES

By B. J. BICKFORD, Liverpool,
MARGARET EGAN and A. GRAHAM BRYCE, Manchester
FROM BROADGREEN HOSPITAL, LIVERPOOL, AND PARK HOSPITAL, DAVYHULME, MANCHESTER

PRIMARY tumours of the heart are uncommon. It is only infrequently that the diagnosis is made during life, and less often still have attempts been made at surgical treatment. As, however, opportunities for the surgical removal of cardiac tumours are likely to become more frequent in the future, it seems both interesting and important to report two cases in which the attempt was made.

CASE REPORTS

Case 1.—John F., aged 4 years, had suffered from loss of appetite for two months, and had been unwell with sweating attacks for four months before that. When admitted to hospital he was in fairly good condition apart from anæmia (hæmoglobin 63 per cent). Dullness to percussion on the left side of the chest suggested a pleural effusion, but a radiograph (*Fig.* 611) showed a large rounded shadow occupying more than half the left hemithorax, mostly situated low down and anteriorly. Paracentesis was unproductive, but led to a tension pneumothorax. He was transferred to a Thoracic Surgical Centre, and improved after air and a little fluid had been removed from the left pleural cavity and he had been given a blood transfusion. X-ray films taken at the time of the pneumothorax revealed the size and shape of the tumour clearly (*Fig.* 612), but the significance of the site of the mass was not appreciated at the time.

Although the diagnosis was in doubt (it was thought to lie between a solid mediastinal tumour, a dermoid cyst, or a pulmonary cyst filled with fluid), surgical exploration seemed clearly indicated before further deterioration in the child's health should take place.

At Operation.—A left thoracotomy was performed (B. J. B.). A very large rounded mass was found in the lower anterior part of the chest, with the phrenic nerve stretched across its surface. The base was so wide that proper access to it could not be obtained, and its bulk could not be reduced by aspiration. Further dissection revealed that the mass was a tumour within the pericardium, and actually arising from the surface of the ventricles of the heart. It was composed of soft pale-brown tissue, resembling muscle in some respects. Many large arteries coursed over its surface and caused troublesome bleeding. There was no pulsation in the tumour mass, presumably on account of its great size. The greater part of the tumour mass was removed, but with some difficulty, for the base was wide and gradually merged into the substance of the heart muscle in the region of the apex of the ventricles. Here no true plane of separation could be found, and the procedure became one of some anxiety, partly for fear of opening into the cavity of the heart, and partly because the manipulation required caused a good deal of irregularity of the heart beat. However, when the separation had been completed, it seemed as if almost all the tumour had been removed.

The child made a good recovery from the operation, and appeared to be restored to normal health and activity. The radiograph (*Fig.* 613) still showed a considerable bulge on the left border of the heart. Although it was at

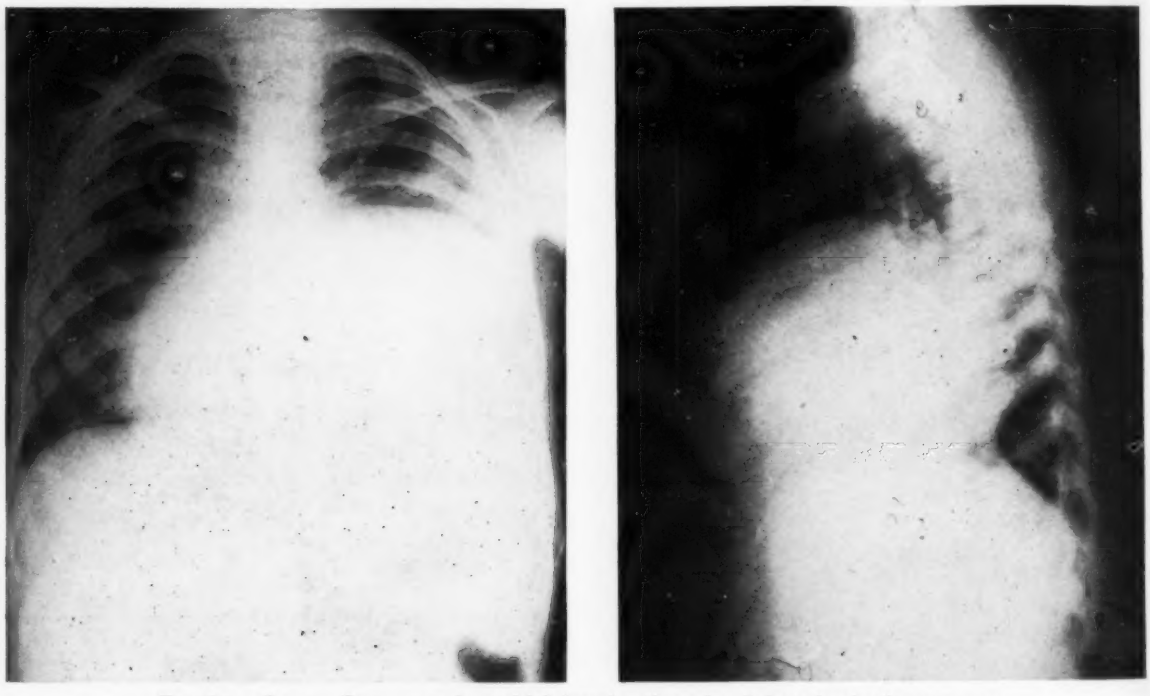


FIG. 611.—*Case* 1. Postero-anterior and left lateral radiographs of chest showing large tumour.

first thought that this was due to intrapericardial blood-clot, it is evident that a considerable mass of tumour was left behind. Twelve months after the operation the child appeared to be perfectly well, but there was an apical systolic murmur, and the radiograph showed that a massive recurrence had taken place. A course of radiotherapy had no effect on the appearances, but the child remained in fairly good health until a rapid decline led to his death two years and two months after the operation. Permission for autopsy was refused.

HISTOLOGY.—The histological appearances of the tumour are unusual and for their description we are indebted to Dr. F. Whitwell. The excised mass was 10 × 7 × 6 cm. in size, resembling a cyst with a shiny outer surface and a ragged cavitated centre (*Fig.* 614). Microscopically (*Fig.* 615) it consists of undifferentiated cells with large nuclei and abundant cytoplasm. In most places there is a sharp differentiation between the individual cells, but in places they fuse into a syncytial

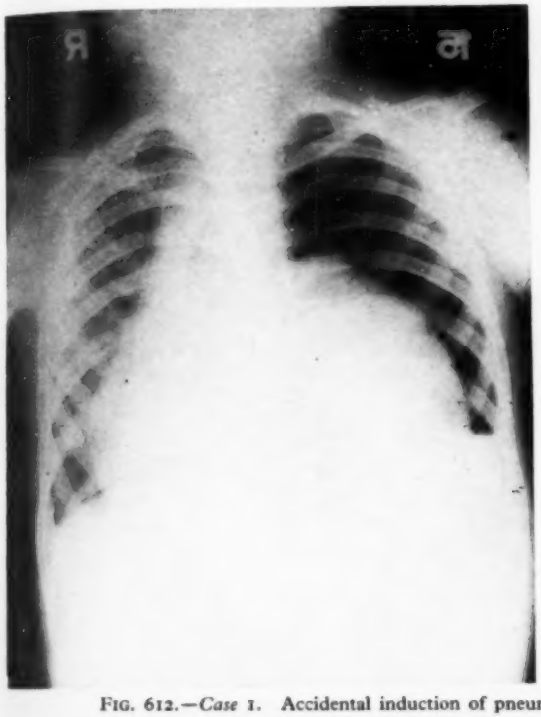
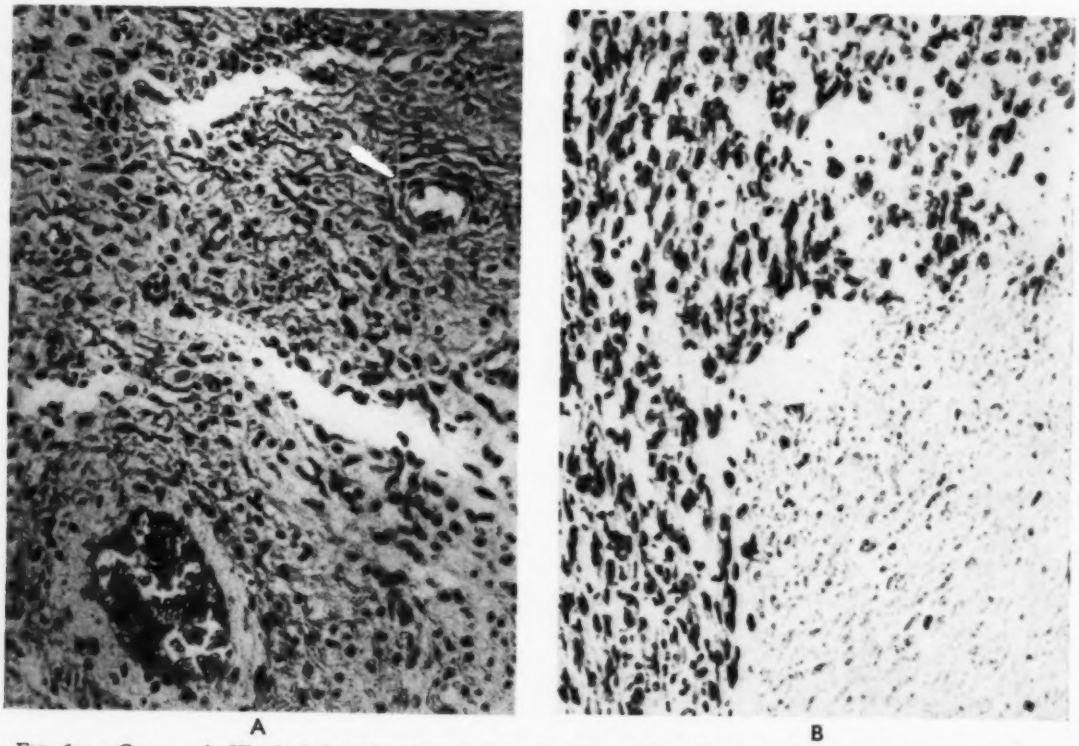


FIG. 612.—*Case* 1. Accidental induction of pneumothorax revealed the position of the tumour more clearly.

FIG. 613.—*Case* 1. Post-operative film.

FIG. 614.—*Case* 1. Appearance of resected tumour. (× ⅛.)

mass. Portions of the tumour are necrotic, but in some places large blood-vessels and fibrous bands cross its surface. There is no striation of the cells, which in some places look rather like thickened synovial membrane. However, the tissue that the tumour most closely



A B

FIG. 615.—*Case* 1. A, Histological section from an area of tumour where blood-vessels penetrate the mass of undifferentiated cells. (Hæmatoxylin and eosin, × 175.) B, Histological section from a more malignant area of the tumour. The cells are more hyperchromatic, and there are necrotic areas. (Hæmatoxylin and eosin, × 235.)

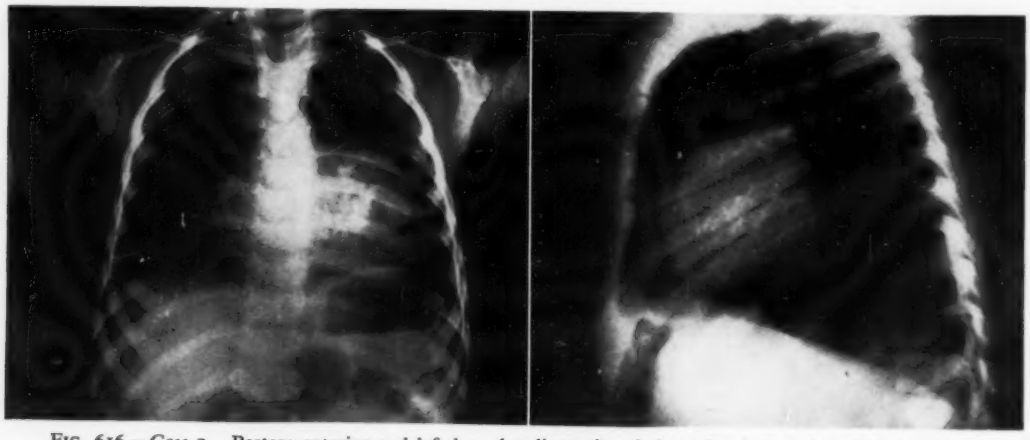


FIG. 616.—*Case* 2. Postero-anterior and left lateral radiographs of chest showing partly calcified tumour.

resembles is undifferentiated mesenchyme. Dr. Whitwell thought that it was a neoplasm rather than a mass due to a developmental anomaly, and he predicted that a recurrence would take place. Although there is no definite evidence of malignancy in the microscopical sections, and there was never any evidence of distant metastasis, the tumour behaved as if it were malignant in its rapid growth after the operation.

Case 2.—Peter L. was first admitted to hospital at the age of 27 months. He had been ill for 36 hours, first with vomiting and later (18 hours) with tachycardia. He had been a premature baby (weight 5¾ lb. at birth) and had had successful conservative treatment for bilateral talipes. On admission, he was normally developed, but extremely distressed, with a pulse-rate of 160 and respiratory rate of 40 per minute. He was pale, but his lips and ears were cyanosed. The heart-sounds were distant, and the neck veins were engorged. The condition was, in fact, one of acute cardiac failure. The pulse-rate rose to 180–220 per minute and the liver enlarged rapidly, reaching the level of the umbilicus on the day after admission. After 56 hours of tachycardia the pulse-rate fell to 120 and there was a dramatic improvement in the general condition.

Eight days after admission a right hemiplegia developed suddenly, without a convulsion or other premonitory symptom. It was thought to be due to a cerebral embolism. There was slow recovery from

this episode and the child was able to walk a month later.

Investigations included a radiograph of the chest, which showed a rounded shadow with some calcification in it projecting from the left border of the heart (*Fig.* 616). Screening showed only transmitted pulsation. Tomography showed that the calcification was deep in the heart muscle. The E.C.G. showed non-specific changes, with high-voltage deflections and deep S waves in leads II and III, with a little depression of the S-T segment in lead I. The Mantoux, Casoni, and Wassermann reactions were all negative. There was a normal blood-count, and an intravenous pyelogram showed no abnormality. There was no radiological evidence of tuberous sclerosis. The diagnosis of a cardiac tumour was made, a rhabdomyoma being thought most probable.

The child remained well apart from an attack of infectious mononucleosis until another episode of acute cardiac failure caused him to be re-admitted to hospital at the age of 3 yr. 2 mth. The pulse-rate was again about 200 per minute, and was of the ventricular type, as shown by the E.C.G. (*Fig.* 617). The tachycardia continued for eighteen days in spite of the administration of quinidine in increasing doses for almost two weeks. It then suddenly dropped to 140, with rapid return of his colour to normal and with cessation of his dyspnœa. During this attack, the liver again enlarged to the umbilicus, but it became impalpable seven days after the remission.

On this occasion an angiocardiogram was carried out with 30 c.c. of 70 per cent diodone. The films (*Fig.* 618) confirmed the presence of a tumour of the heart. It caused displacement of both ventricles to the right and a filling defect could be clearly seen in the left ventricle. The appearances indicated that the tumour was arising posterosuperiorly on the left side of the heart, probably from the left ventricle. It seemed to be a mass with well-defined borders rather than one spreading diffusely in the heart musculature.

It seemed likely that the complications of acute heart failure and cerebral embolism would recur unless the tumour were removed, and operation was therefore undertaken when the child was 4 yr. 3 mth. old.

AT OPERATION.—A left anterior thoracotomy (A. G. B.) was performed, and when the pericardium had been opened a rounded tumour about 4·5 cm. in diameter was found to be arising from the region of the left atrio-ventricular groove. There were also several white nodules about 5 mm. in diameter on the surface of the heart along the line of the descending branch of the left coronary artery. The heart was very irritable, and there were several bursts of ventricular tachycardia, very evident on the E.C.G. tracing, which lasted for as long as 3 min. The tumour was firmly embedded in the muscle of atrium and ventricle and its removal was manifestly impossible. It was not thought to be justifiable to risk further tachycardia by attempting to remove tissue for biopsy, and the precise nature of the tumour therefore remains unknown. The child made an uninterrupted recovery from the operation.

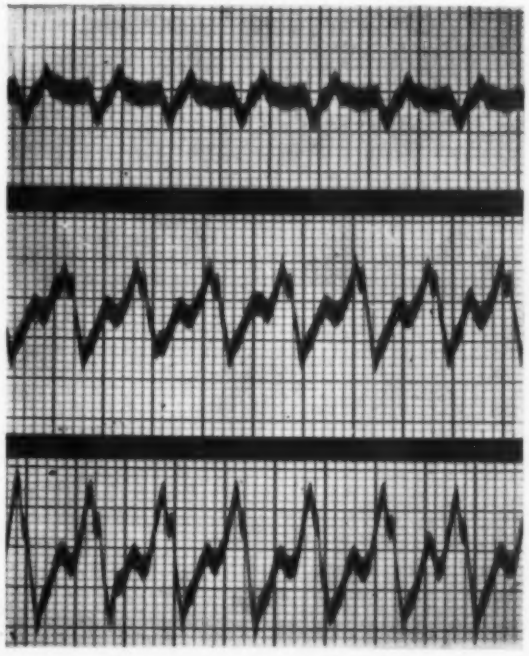


FIG. 617.—*Case* 2. E.C.G. tracing showing ventricular tachycardia.

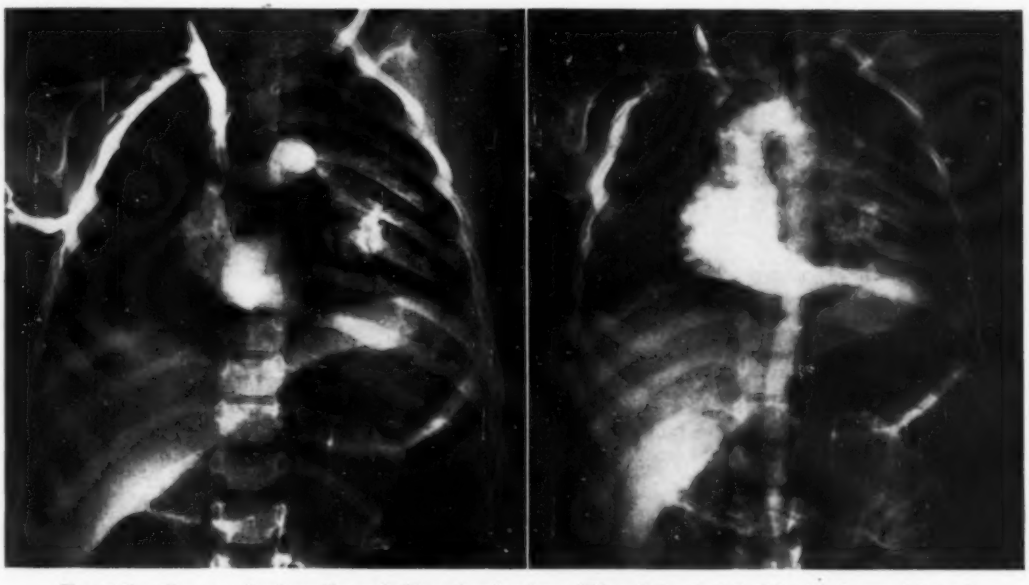


FIG. 618.—*Case* 2. Angiocardiograph films showing large filling defect in left side of left ventricle and corresponding with the position of the tumour mass.

He remained perfectly well for 2½ years, when another attack of acute cardiac failure due to tachycardia necessitated further hospital treatment. This attack was less severe than the previous ones, and the tachycardia ceased 48 hours after admission. On this occasion he was treated with procaine amide (pronestyl) given orally in 2-hourly doses increasing from 0·125 to 1·0 g. Whether

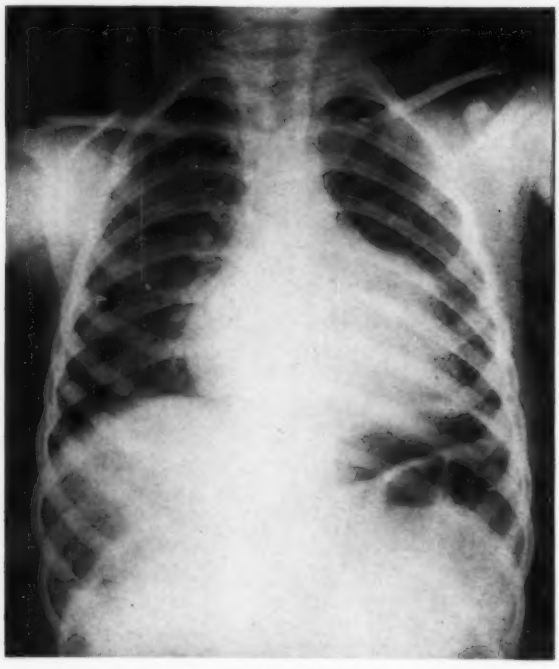


FIG. 619.—*Case* 2. Radiograph of chest at 7 years of age. There is little change in the size of the tumour relative to the heart.

the procaine amide on this occasion, or the quinidine on the previous one, had any effect on the cessation of the tachycardia seems on the whole doubtful. The boy's recovery was as rapid as before.

A radiograph (*Fig.* 619) at 7 years of age showed that the tumour had remained about the same size relative to that of the heart.

This patient died suddenly, quietly at his desk in school at the age of 8 years 6 months.

AT AUTOPSY (*Fig.* 620).—We are indebted to Dr. Keith S. Daber for the following notes :—

Cardiovascular system: The aorta and coronary arteries were healthy ; the pericardial cavity was generally obliterated by old fibrous adhesions. The heart (weight 9 oz.) was much enlarged and on its anterior surface could be seen a rather ill-defined slightly raised and rounded swelling about 4½ cm. in diameter. The surface of the swelling showed occasional small grey nodules ; on section this mass consisted of firm greyish white tissue which extended over an area 5 × 4 × 4 cm. ; it involved the whole thickness of the anterior wall of the left ventricle near its base, but did not appear to be affecting the interventricular septum or the right ventricle ; the tumour was not apparently encapsulated ; it was partially calcified. The left auricle was displaced backwards, but otherwise there was no abnormality in the heart ; all the heart valves were healthy.

Urinary system: Both kidneys were of normal size and shape and their capsules stripped easily, leaving a smooth surface. The upper pole of the left kidney was occupied by a unilocular smooth-walled cyst, 4 cm. in diameter, containing colourless watery fluid ; the cyst was not connected with the pelvis of the kidney ; leading from it there was a grossly dilated (1 cm. diameter) tortuous ureter which ended blindly at the entrance of the bladder ; the other ureter to the left kidney was in its normal position and appeared normal. The kidneys otherwise showed no abnormality apart from congestion.

Central nervous system: The brain was somewhat œdematous ; externally there was no abnormality ; on

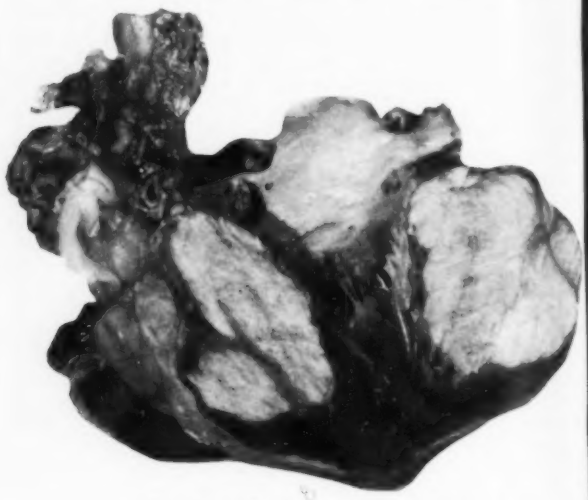


FIG. 620.—Section through the heart.

section, on the left side, affecting the internal capsule, lentiform nucleus, and external capsule and claustrum, there was an old liquefied infarct 2 cm. in diameter. The cerebellum and brain-stem were normal. There was no evidence of grey nodular thickenings which are seen in cases of tuberous sclerosis.

The *respiratory system* and *alimentary system* showed no abnormality.

Histologically the tumour was a highly collagenized fibroma showing a few small areas of calcification ; special stains for glycogen and striped muscle were negative.

The small nodules seen under the pericardium at operation were well seen post mortem and were irregularities on the surface of the tumour.

DISCUSSION

There is a considerable literature on the subject of tumours of the heart, and in an authoritative review of the reported cases Prichard (1951) collected descriptions of 415 primary tumours. More than 75 per cent of the primary tumours are myxomas (G. 125 cases) or sarcomas (113 cases). As is well known, the myxomas are polypoid subendocardial masses which usually arise in the left atrium and tend to cause obstruction of the mitral valve. The sarcomas arise in the heart muscle and are apparently rather more frequent on the right side of the heart, where they may cause obstruction of the superior vena cava. They are chiefly of the round-cell or spindle-cell type, but rhabdomyosarcomas and angiosarcomas also occur. The remainder of the tumours fall into the groups of rhabdomyoma, hamartoma, or fibroma (with varying combinations of overgrowth of naturally occurring tissues), lipoma, and epithelial inclusions which are usually cystic and which do not appear to be true tumours.

Whether the rhabdomyomas are true tumours is disputable and it is far from easy to understand their nature. They appear often to be part of a complex

developmental anomaly in which, in addition, cysts and solid tumours may be found in the pancreas and kidneys, together with angiolipomas in the liver, and adenoma sebaceum in the skin. The cerebral lesions of tuberous sclerosis are also frequently present. The lesions in the heart are usually multiple, but sometimes there is a single nodule, usually near the apex of the heart. A very rare diffuse form is also described which it is difficult to distinguish from simple hypertrophy macroscopically. It appears that many rhabdomyomas regress with the passage of time (Mahaim, 1945; Prichard, 1951).

The first case which we report here appears to be a tumour of an unusual nature. It consists of cells apparently developed from the embryonic mesenchyme. It must probably be regarded as a form of sarcoma. The second case presents a greater problem. There are no convincing features which enable an opinion on the nature of the tumour to be formed. The fact that there were other nodules on the surface of the heart is a point in favour of its being a rhabdomyoma, but on the other hand a comparatively large tumour with radiological evidence of calcification in it is not like those rhabdomyomas which have been previously described. One should perhaps note the case described by Crowell and Rice (1950) in which a " large encapsulated tumour mass " was recorded. It had several hæmorrhagic areas in it, and it seems not impossible that the calcification noted in our case had followed hæmorrhage in early life. The lapse of five years since the first symptoms in this case seems to rule out the possibility of malignancy, and without being able to be sure of the diagnosis we feel that a rhabdomyoma is probably the most likely one.

Arrhythmia and Cardiac Neoplasms.—There are three recorded cases in which cardiac arrhythmia in infants has been associated with tumours of the heart. Wegman and Egbert (1935) discovered a rhabdomyomatous process in the heart of a 10-months' old child who had died from auricular flutter. One nodule was found in the interventricular septum and was thought to have interfered with the conducting system of the heart. Crowell and Rice (1950) reported a rhabdomyoma, and Sussman and Stasney (1950) described a glycogenic tumour which had been found in infants' hearts at autopsy. Both had been associated with cardiac arrhythmia. Our second case appears to be the first reported case in which a heart tumour causing arrhythmia has been diagnosed during life.

Surgical Treatment.—There are few reports in the literature of attempts at removal of cardiac tumours. Beck (1942) described the removal of an intrapericardial teratoma, and, in another case, a calcified cyst from the heart. Gebauer (1943) was unfortunate in that an accidental injury to the aorta prevented him from removing a huge intrapericardial teratoma. Hochberg and Robinson (1950) removed a primary cavernous hæmangioma of the pericardium which involved a part of the myocardium, and Maurer (1952) removed a large pedunculated lipoma from the surface of the left ventricle. Longino and Meeker (1953) were able to excise most of a huge sarcoma from the heart of an infant three months old but recurrence led to the child's death not long afterwards. The cases which we record appear to be the fifth and sixth in which removal of a cardiac tumour has been attempted.

The technical problems of removal of a cardiac cyst—e.g., the case of Beck (1942), and the cardiac hydatid cysts reported by d'Abreu (1950) and Windsor (1954), who quotes the successful removal of such a cyst by Long in 1932—are similar to those encountered in removal of an actual tumour. The almost insuperable difficulty which arises when tumour has a broad base in the myocardium presumably does not arise in the case of a hydatid.

No doubt many further attempts will be made at excision of cardiac tumours. The degree of success to be expected depends chiefly on the nature and site of the tumour. It seems likely that only innocent and reasonably well-pedunculated tumours will be capable of complete extirpation, as it is difficult to imagine that it will ever be possible to remove any considerable section of the wall of one of the chambers of the heart. A possible exception would be if the growth should arise in an auricular appendage. The pedunculated intracardiac myxoma presents a special problem which will certainly have to be faced more often in the future during the surgical treatment of patients with mitral valve disease, but it is not one with which we are concerned here.

It is evident that successful surgery of heart tumours is more likely when the nature of the condition has been realized before operation. A rounded shadow in a chest X-ray film, merging with the heart shadow in the lower anterior part of the chest, should give rise to the suspicion that a heart tumour is present. Of all special methods of investigation, angio-cardiography seems to be the one most likely to give positive information as to whether the mass is arising in the heart. In an infant paroxysmal tachycardia should also give rise to the suspicion of the possibility of rhabdomyomatosis, even if there is no radiological evidence other than cardiac enlargement to be found (Miller, 1954).

Although surgery may often not be successful in cases of cardiac tumour because of the anatomical conditions found at operation, it seems to us to be beyond controversy that the attempt to remove it should be made if the diagnosis is suspected.

SUMMARY

Two cases of tumour of the heart occurring in children are reported. Both were treated by surgical operation, but it was not possible to remove either tumour completely.

The literature is briefly reviewed, with special reference to surgical treatment.

We should like to thank Dr. F. Whitwell for the histological report and for the photomicrographs of *Case* 1; also Dr. A. Morgan Jones for his help with the radiology in *Case* 2, Dr. Brian Locke for the angiocardiogram, Dr. R. G. Ollerenshaw for the reproductions of the X-ray films in this case, and Mr. W. Lee of the Central Photographic Dept., University of Liverpool, for the X-ray reproduction and photograph of the specimen in *Case* 1.

REFERENCES

BECK, C. S. (1942), *Ann. Surg.*, **116**, 161.
CROWELL, W. M., and RICE, E. C. (1950), *Clin. Proc. Child. Hosp. Wash.*, **6**, 292.
D'ABREU, A. L. (1950), *Thorax*, **5**, 362.
GEBAUER, P. W. (1943), *J. thorac. Surg.*, **12**, 458.
HOCHBERG, L. A., and ROBINSON, A. I. (1950), *Circulation*, **1**, 805.
LONGINO, L. A., and MEEKER, I. A., jun. (1953), *J. Pediat.*, **43**, 724.
MAHAIM, I. (1945), *Les Tumeurs et les Polype[illegible] du Cœur*. Paris: Masson et Cie.
MAURER, E. R. (1952), *J. thorac. Surg.*, **23**, 47[illegible].
MILLER, R. A. (1954), *Pediat. Clin. N. Amer.*, Feb., 1954, 51.
PRICHARD, R. W. (1951), *Arch. Path. (Lab. Med.)*, **51**, 98.
SUSSMAN, W., and STASNEY, J. (1950), *Amer. Heart J.*, **40**, 312.
WEGMAN, M. E., and EGBERT, D. S. (1935), *J. Pediat.*, **6**, 818.
WINDSOR, H. M. (1954), *Brit. J. Surg.*, **41**, 541.

INTERDIGITAL SINUSES IN BARBER'S HAND

BY H. D. W. POWELL

SURGICAL REGISTRAR, THE ROYAL LONDON HOMŒOPATHIC HOSPITAL, LONDON

A RECENT comprehensive review of this subject by Currie, Gibson, and Goodall (1953) added 11 of their own cases to 18 previously published cases. Both they and other writers have commented that many cases have probably either failed to come for treatment, or have not been recorded. Accordingly it is felt that a further case should be put on record, especial note being made of one or two unusual features.

CASE REPORT

H. K. came to the Casualty Department on April 12, 1954, complaining of a small swelling in the cleft between his left index and middle fingers. The day previously he had noticed a black spot at this site, and on closer inspection had seen some short hairs, which he had extracted.

ON EXAMINATION.—He was found to have a small sinus opening in the interdigital cleft with a slight swelling on the dorsum of the hand, proximal to this cleft (*Fig.* 621). There was no inflammation, only slight tenderness, and no glandular enlargement was found on the affected side. No other similar findings were present elsewhere in either hand, nor had there been any similar previous history. Aged 54, he had been a barber for nearly forty years. He did not know of any similar occurrence in any of his fellow barbers. The diagnosis was confirmed by the injection of 1 c.c. of Viskiosol Six (Diodone Viscous Solution — May & Baker) through a lacrimal duct cannula inserted into the sinus opening, and antero-posterior and lateral radiographs were then taken (*Fig.* 622). Following the suggestion of Hueston (1952) that some of these cases might resolve completely with conservative treatment by means of adequate protection during working hours, the affected cleft was covered with

FIG. 621.—Photograph of hand at first attendance.

a small waterproof dressing (Dalmas); he was instructed to wear one of these each day while at work, and given sufficient dressings to last for a month. Re-examined on May 11 he stated that three days previously a further opening had appeared about 1 cm. proximal to the

FIG. 622.—Radiograph of hand showing sinogram.

original sinus. This was towards the dorsum of the hand and more over the known site of the interdigital cavity. The patient was admitted for hand toilet and given a pre-operative course of penicillin, as it was quite obvious that no progress was being made with conservative treatment, and surgical excision would have to be undertaken.

AT OPERATION (May 13).—Under general anæsthesia (Dr. G. Way), with the aid of a pneumatic tourniquet on the upper arm, a small quantity of methylene blue was injected into the more recent sinus opening, again by means of a lacrimal duct cannula. An elliptical portion of skin surrounding the two openings was then excised, together with the whole of the blue-outlined sinus. One short hair was found lying in the excised cavity. The wound was closed with interrupted black thread sutures, after dusting with penicillin-sulphanilamide powder, without drainage.

Sutures were removed on the eleventh post-operative day; the wound, not yet fully healed, was covered with a dry dressing, and the index and middle fingers were bound together with strapping. On the eighteenth post-operative day the wound was fully healed, and he was sent back to work with instructions to cover the wound with protective dressings for the next few days. He was seen again a month later at his work and was delighted with the result.

HISTOLOGICAL REPORT (Dr. L. W. Proger).—The section shows a fragment of hair (doubly refractile) surrounded by foreign-body giant cells embedded in chronic inflammatory granulation tissue, which formed the lining of the sinus. (*Fig.* 623.)

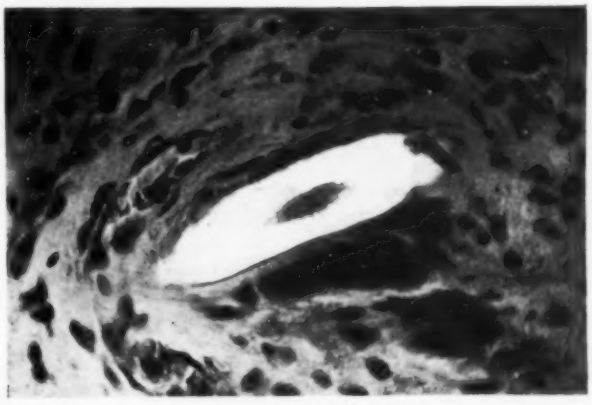


FIG. 623.—Photomicrograph of section from lining of sinus. (× 400.)

COMMENT

Currie, Gibson, and Goodall (1953), whose recent paper has already been referred to, deal fully with the previously reported cases and discuss in detail the aetiology and pathology of this condition. No attempt is made here to deal with the debated question of the relationship between these hand sinuses and those classically named pilonidal, but the case under review is clearly acquired in nature. Conservative treatment was tried in this case and found wanting; sugical excision has given an entirely satisfactory result with a relatively short period off work.

SUMMARY

A further case of interdigital sinus in a barber's hand is briefly reported. Attention is drawn to the use of a radio-opaque dye in outlining the sinus cavity, a method to which no previous reference has been found. Conservative treatment was tried and failed, while surgical excision was successful.

I am very grateful to Mr. Harold Dodd, under whose care this man was admitted, for his advice and for permission to publish this report. I would also like to thank the Department of Clinical Photography of the Hospital for Sick Children for the clinical photographs, and Dr. L. W. Proger, of the Royal College of Surgeons, for the pathological report and photomicrograph.

BIBLIOGRAPHY

CURRIE, A. R., GIBSON, T., and GOODALL, A. L. (1953), *Brit. J. Surg.*, **41**, 278.
DOWNING, J. G. (1952), *J. Amer. med. Ass.*, **148**, 1501.
HUESTON, J. T. (1952), *Aust. N.Z. J. Surg.*, **21**, 226.

EXPERIMENTAL SURGERY

THE INHIBITORY ACTION OF LOCALLY APPLIED ANTIHISTAMINES ON CANINE ACID GASTRIC SECRETION INDUCED BY HISTAMINE

By A. W. KAY and A. P. M. FORREST

UNIVERSITY DEPARTMENT OF SURGERY, WESTERN INFIRMARY, GLASGOW

Histamine, when given parenterally, is a powerful stimulus for secretion by the parietal cells of the gastric glands. This secretagogue effect is not abolished when the gastric mucosa is deprived of its extraneous nerve-supply. Thus histamine appears to act directly on the parietal cell or at least very close to it.

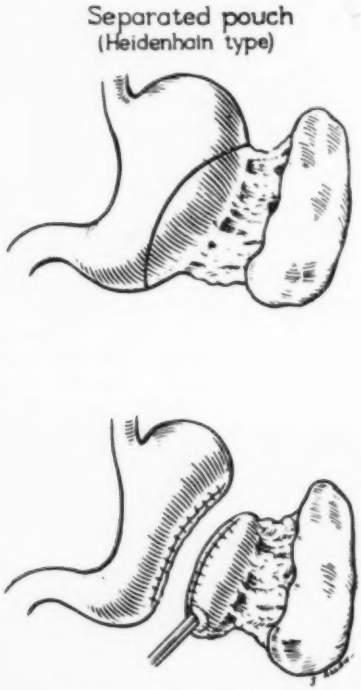


Fig. 624.—A separated gastric pouch of Heidenhain type.

The antihistamine group of drugs inhibit the action of histamine in all its other pharmacological effects, but not in its effect on the parietal cells. This anomalous action has made it difficult to accept the view that histamine plays a vital role in acid secretion under physiological conditions. Suspecting that the anomaly might be due to failure of the antihistamine to reach the parietal cells in adequate dosage, we devised the following experiments in which, in dogs, the antihistamine is applied locally by instillation into a separated gastric pouch.

METHOD OF STUDY

Four dogs with separated pouches of the stomach (Heidenhain type) were used (*Fig.* 624). The animals were fasted for a period of not less than sixteen hours prior to the performance of each test. The standard histamine test adopted was the secretory response of the pouches over a two-hour period to the subcutaneous injection of 0·05 mg. histamine base per kg. body-weight. Juice was collected at intervals of 15 minutes, the volume of each sample measured and the concentration of free acid determined by titration with tenth normal sodium hydroxide, using Topfer's solution as indicator.

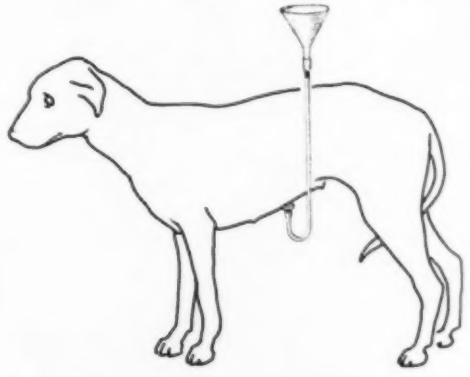


Fig. 625.—Diagram to demonstrate method of irrigation of pouch.

From these determinations, the output of free acid in milliequivalents can be calculated.

The effect of locally applied antihistamines on this secretory response was determined by irrigating the pouch with the test solution during a half-hour period prior to the histamine injection. A funnel and tube was filled with the solution and connected to the cannula draining the pouch (*Fig.* 625). The natural motility of the pouch ensured efficient irrigation, the level of the irrigating fluid in the funnel oscillating with each regular contraction of the pouch. Following this half-hour period of irrigation the pouch was allowed to drain for five minutes when histamine was injected and collection of secretion begun.

The solutions of antihistamines tested were promethazine hydrochloride in concentrations of 1, 2, 4, and 6 mg. per ml. 0·9 per cent saline, and mepyramine maleate in a concentration of 2 mg. per ml. None of the solutions used had significant acid buffering capacity. In a control series of tests the pouch was irrigated with 0·9 per cent saline alone.

The output of hydrochloric acid secreted for the two-hour period following the injection of histamine was calculated for each test. When a statistical comparison of results was desired the values obtained for each dog were standardized by expressing the acid output as a percentage of the maximal output of that pouch when stimulated by histamine. The

maximal output to repeated subcutaneous injections of histamine was determined by the method of Code, Blackburn, Livermore, and Ratke (1949) on three occasions on each dog. The logarithm of these percentages follow a normal distribution (Forest and Code, 1954) and so can be used for analysis. Percentages of less than 1 per cent were expressed as zero on the logarithmic scale. The probable significance of the difference between the acid outputs expressed in this way was established by an analysis of variance.

In a separate group of experiments pouch motility was recorded during irrigation, by connecting the system to a tambour-kymograph unit.

RESULTS

The previous irrigation of the pouches with physiological saline was without effect on the secretory response to the standard dose of histamine

Table I.—Effect of Saline Irrigation on the Mean Secretory Response of Heidenhain Pouches in 4 Dogs to a Standard Dose of Histamine (0·05 mg./kg.) over a 2-Hour Period

	No. of Tests	*2-Hour Output HCl in response to Histamine. Per cent of Maximal Output*	*P log*
No irrigation	16	25·0	> 0·5
Irrigation with 0·9 per cent saline	12	21·4	

(*Table I*). On the other hand, a decisive depression in the secretory response followed irrigation of the pouch with promethazine. The degree of inhibition

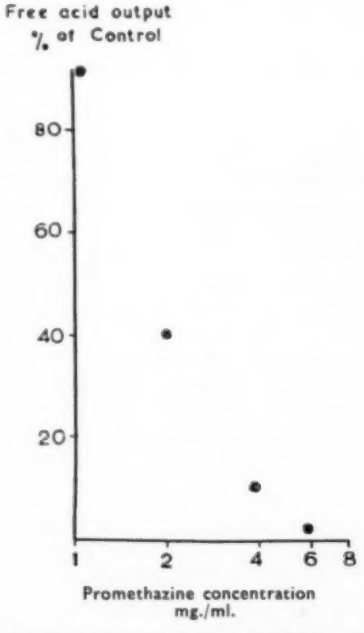


Fig. 626.—Graphic relationship of inhibition of histamine induced secretion to the logarithm of the dose of promethazine. (Mg. per ml. irrigating solution.)

increased as the concentration of promethazine in the irrigating fluid was increased and was ultimately complete in three of the four dogs studied (*Table II*). The mean percentage inhibition for all the dogs produced by the different concentrations of promethazine was calculated. Graphic representation demonstrated that the degree of inhibition was related in a linear fashion to the logarithm of the dose of promethazine (*Fig.* 626).

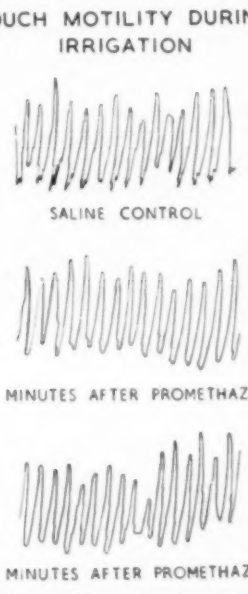


Fig. 627.—Diagram illustrating the effect of promethazine irrigation on pouch motility. Recorded by tambour-kymograph unit connected to irrigating system.

Comparison of the inhibitory effects of an equal concentration of promethazine and mepyramine on the secretion induced by histamine clearly

Table II.—The Effect of Locally Applied Promethazine on the Output of Free Hydrochloric Acid in Milliequivalents Secreted in Response to Histamine (0·05 mg./kg.) from Separated Pouches in Dogs. Each Result Represents the Mean of 3 Tests

	MEq HCl secreted in 2-hour Period after Histamine 0·05 mg./kg.				
Dog	*Irrigation with 0·9 per cent Saline*	*Irrigation with Promethazine in Saline*			
		1 mg./ml.	*2 mg./ml.*	*4 mg./ml.*	*6 mg./ml.*
A	0·234	0·091	0·083	0·000	0·000
B	1·872	1·420	0·466	0·107	0·000
C	1·621	1·316	1·017	0·446	0·156
D	0·807	1·183	0·304	0·054	0·000

demonstrates that, of the two, promethazine is the more potent inhibitor (*Table III*).

The spontaneous motility of the pouch was not reduced during irrigations with promethazine

Table III.—A Comparison of the Inhibitory Effect of the Local Application of Promethazine and Mepyramine on the Secretory Response to Histamine from Heidenhain Pouches in 4 Dogs

Irrigating Solution 2 mg./ml.	*No. of Tests*	*2-Hour Output HCl in response to Histamine. Per cent of Maximal Output*	*P log*
Promethazine	12	8·9	< 0·02
Mepyramine	12	16·2	

(6 mg./ml.) (*Fig.* 627). This solution caused complete inhibition of histamine-induced acid secretion in three of the four dogs.

DISCUSSION

In an exhaustive review of the literature Code (1951) concluded that the synthetic antihistamines administered orally or parenterally, while capable of blocking the systemic effects of histamine, fail to block its action on the parietal cells. Our results show, however, that the antihistamines, as exemplified by promethazine and mepyramine, do exert a blocking action on the parietal cells when applied directly to the gastric mucosa. Complete inhibition of the acid response to histamine can be effected by increasing the concentration of the antihistamine in the irrigating solution. Before considering the implications of this finding it is essential to ascertain that the inhibition of acid secretion is due to a true antihistamine action.

In a similar study on dogs with vagally denervated pouches of the entire stomach, Robertson and Grossman (1952) observed inhibition of histamine-stimulated acid secretion when the pouch was irrigated with a solution of an active antihistamine. A direct irritant effect on the gastric glands rather than a true antihistamine effect was considered to be the likely mechanism of this inhibition. The concentration of their antihistamine solutions was considerably greater than in the present study and it may well be that an irritant effect had a role in reducing acid output. However, the nature of the dose–response curve shown in *Fig.* 626 indicates that we have observed a true pharmacological effect.

The synthetic antihistamines, in addition to their principal activity in antagonizing histamine, are known to possess other pharmacological actions which may have influenced the acid response to injected histamine in our experiments. Firstly, the antihistamines are local anæsthetics. There is not, however, a quantitative relationship between local anæsthetic activity and antihistamine activity. Promethazine is more potent than mepyramine in its antihistamine activity (Bain, 1949) while both have similar local anæsthetic potencies. The fact that our results demonstrate that promethazine is the more active inhibitor of acid secretion provides reliable evidence against any local anæsthetic activity being the main pharmacological action involved. Secondly, the antihistamines possess an atropine-like action which might conceivably reduce the acid output of the gastric mucosa to histamine stimulation. However, this atropine action is known to be slight and almost certainly insufficient to inhibit completely the secretory response of the pouch mucosa. We have shown that promethazine in a concentration of 6 mg. per ml., though capable of inhibiting completely the secretion of acid in response to histamine, does not depress the motility of the pouch. An atropine-like action sufficient to inhibit acid secretion would also inhibit smooth muscle activity.

It appears, therefore, that the parietal cell receptor site, like all other histamine-sensitive receptors, can be blocked by the synthetic antihistamines and that this block is not the result of local anæsthetic or atropine-like activity. This observation does not dispose of the anomaly which provoked this investigation; the failure of parenterally administered antihistamines to antagonize histamine at the parietal cell remains unexplained. A simple explanation is that injected antihistamine does not arrive at the acid secreting cell in adequate concentration to abolish the action of histamine. It must be admitted, however, that the same concentration is capable of blocking at smooth muscle receptors, preventing all the systemic effects of large doses of injected histamine while permitting the gastric mucosa to secrete acid at maximum output levels. This has been strikingly demonstrated by Halpern (1948). He has shown that, although guinea-pigs could be protected against the systemic effects of as much as 1500 lethal doses of histamine, many died within forty-eight hours as a result of gastric perforation. It seems unlikely, therefore, that the anomaly is to be explained on the basis of an ineffective antihistamine concentration in the vicinity of the parietal cell. It is now known that certain enzyme systems are very highly specific even as to point of attack. The parietal cell enzyme system may prove to be in this category—immune to antihistamine in the blood-stream but vulnerable to locally absorbed antihistamine.

The inhibitors of gastric acid secretion in common clinical use depend on blockade of neurally transmitted stimuli for their gastric effects. Demonstration of histamine block at the parietal cell is of great interest in that we are presumably observing inhibition of acid secretion by the stomach at parietal cell level. The effect of locally applied antihistamines on the chemical and nervous phases of acid secretion clearly merits investigation; if inhibition can be demonstrated, further evidence will have been provided in support of the hypothesis that histamine participates normally in the secretion of acid by the stomach.

SUMMARY

The secretory response of separated canine pouches to a standard dose of histamine was studied following the direct application of antihistamines to the mucosa of the pouch.

Both promethazine hydrochloride and mepyramine maleate were found to inhibit the acid secretion induced by histamine, and, of the two, promethazine was the more potent inhibitor.

It is concluded that the mechanism of this inhibition is a true antagonism to histamine and not a local anæsthetic or atropine-like action.

REFERENCES

BAIN, W. A. (1949), *Lancet*, **2**, 47.
CODE, C. F. (1951), *Pharmacol. Rev.*, **3**, 59.
— — BLACKBURN, C. M., LIVERMORE, G. R., jun., and RATKE, H. V. (1949), *Gastroenterology*, **13**, 573.
FORREST, A. P. M., and CODE, C. F. (1954), *Amer. J. Physiol.*, **177**, 425.
HALPERN, B. N. (1948), *Arch. int. Pharmacodyn.*, **74**, 314.
ROBERTSON, C. R., and GROSSMAN, M. I. (1952), *Ibid.*, **90**, 223.

STUDIES IN RESTORATIVE GROWTH PROCESSES IN MAMMALIAN WOUND HEALING

By H. A. S. VAN DEN BRENK

H. N. SMITH RESEARCH FELLOW, DEPARTMENT OF APPLIED PHYSIOLOGY, ROYAL COLLEGE OF SURGEONS OF ENGLAND

INTRODUCTION

The restoration of body form which takes place following tissue injury and loss is identified by a variety of pathological terms, such as restitution, regeneration, reconstitution, and repair, which have been used to classify various types of wound healing and allied phenomena. The confusion, which attaches to the usage of a particular term, for a specific example of restoration, mainly arises from qualitative differences in the tissues which replace the damaged zone, or fill in the region of total tissue loss. However, the common factor essentially lies in the implication that healing, by definition, is always accompanied by a positive growth, to a greater or lesser degree, and with Morgan (1901) it seems legitimate to use the general term ' regeneration ' to define the phenomenon of positive growth. The tissues which abrogate the spatial discontinuity in body form, resulting from injury, may be termed the ' regenerate ' or ' blastema '. A phylogenetic study of wound healing and allied phenomena clearly indicates that two essential means of regeneration have evolved in the organism, namely *morphyllaxis*, or a general remodelling of the remaining portion of the body to restore the whole form, and *epimorphosis*, or the direct redevelopment in situ of tissues which may or may not measure up, qualitatively and quantitatively, to the tissues lost (Needham, 1952). Whilst morphyllaxis predominates in lower invertebrates, and the development of body rigidity and the evolution of the exoskeleton and the bony skeleton has given emphasis to epimorphosis as the means of regeneration in higher animals, it is illogical to attribute a particular evolutionary status to either process. Regeneration in protozoa and cœlenterates is often a pure epimorphic phenomenon, whilst the compensatory hypertrophy which takes place in the mammalian liver is clearly more closely related to morphyllaxis. A combination of epimorphosis and morphyllaxis, in regenerative processes, occurs more frequently than either process alone.

The tissue mobility that prevails in a particular site is of considerable importance in determining whether or not a blastema is strictly locally recruited. The dominance of migration in wound closure has been confirmed by extensive experimental evidence, particularly for epithelial tissues (*see below*). As Medawar (1945) has stressed, " the *tactics* of regeneration, as of embryonic development, is primarily and fundamentally a matter of movement of cell substance, cells, and cell groups. It is not primarily a matter of cell division, or of synthesis in general, though in due course these are called upon to play their part ". The imposition of mechanical embarrassments on tissues, which are already subjected to a threshold stimulus which initiates regeneration, influences the distribution and movement of cells and cell groups. Not only is the tempo of the healing process affected, but the curve of growth is modified. In general, morphyllaxis is a much more rapid means of restoration than epimorphosis, and should the ratio between the two means of blastema recruitment alter according to the situation of the wound, and the tissue mobilities prevailing, or to artificially created stresses, then the curves of growth which have been deduced from data on wound healing find no specific application to the phenomenon in hand, and fail successfully to predict the healing of wounds from a practical standpoint.

A further factor, which is related to cellular kinetics, and dominates the movement of cells in metazoan forms, is that of organization and the recognition of cell patterns (or organs) and mutual interdependence of tissues. The physicochemical factors underlying organization at a cellular level have given rise to biological conceptions such as organizers, fields, gradients, etc. However valid and informative it may be to particularize these aspects, it is no less apparent that intercellular contact and proximity in the organized tissue determines to a large extent the ability of a cell to move (migrate). In a similar way, the resting shape of a cell is determined in no small measure by differential stresses and strains to which it is subject (D'Arcy Thompson, 1942). The conception of cell shape in relation to states of physical equilibrium, polar furrow, and *areæ minimæ* arises from a consideration of the form of cellular aggregates. D'Arcy Thompson has drawn attention to the fundamental generalization of Sachs that " the manner in which cells divide is the *result* and not the cause of the form of the dividing structure : that the form of the mass is caused by its growth as a whole and is not a resultant of the growth of the cells individually considered ". These considerations are particularly pertinent in regard to growth curves of cell aggregates and the relation of methods of mensuration to the documentation of data (*see below*).

The considerations, which have been briefly stated, fundamentally apply to the study of healing of wounds with tissue loss, in the mammalian integument. Quantitative studies have largely dealt with establishing growth curves for the sum of the regenerative mechanisms concerned, irrespective of whether restoration of body form is due to processes akin to epimorphosis or morphyllaxis. The resultant growth curve applies only to a particular wound of determinate size and shape, at a particular site in a given species. The mathematical expression of a growth curve empirically derived from a given set of data fails to fit other examples of wound healing satisfactorily, and does not provide any biological truths as to the nature of the process-deductions also substantiated by other considerations (Medawar, 1947 ; Gray, 1929). However, it has been stated that wound healing is perhaps the most specific type of reaction presented by living organisms, and that all wounds heal in the same fashion, a fixed pattern

being followed (Cameron, 1952). This generalization is only true in the widest sense, in so far as we recognize that certain basic phenomena occur—migration, morphyllaxis, epimorphosis, etc. Also, for a given type of organism, certain fairly well-defined morphological processes can be identified; in the case of mammalian wounds of the integument the outstanding common features are the contraction of the tissues surrounding the wound, the regeneration of epithelium, and the regeneration of a complex tissue called 'granulation tissue'. All three processes clearly play a part in the healing of all wounds of the mammalian integument, although the quantitative importance of each component is subject to wide variations. In large wounds of soft mobile skin, the reduction of spatial discontinuity is largely due to contraction. Wounds in rigid sites heal by the local growth of granulation tissue and epithelium.

It follows that a curve of growth for the individual components of the healing process—namely, contraction, epithelial regeneration, and growth of granulation tissue—provides information more applicable to wound healing in general than that provided by a curve of growth which ignores individual contributions to the growth process. This is particularly evident in dealing with the elucidation of factors concerned in the promotion or retardation of wound healing, e.g., bio-assay studies. It is also undeniable that the practical difficulties which attend the measurement of exposed wounds are of no small order. It is difficult to understand how measurements of healing under a scab can be made with any accuracy; the difficulties which beset the determination of an end point for epithelialization alone leads to large quantitative errors.

The present study relates to quantitative and qualitative aspects of wound healing, utilizing experimental data determined by measuring the growth of epithelial regeneration and granulation tissue formation, using closed-chamber techniques in rabbits' ears, and the direct measurement of contraction in wounds of rabbits' skin. Before setting out the protocols of experiments, and the results, it is desirable to discuss and formulate certain conditions for methods of mensuration adopted in wound healing and to determine a method of measurement which can be validly and consistently applied to the growth of the various regenerates in wounds of different type, shape, and size.

Mensuration of Growing Tissues.—The measurement of growth of cell populations is fraught with many difficulties, particularly in dealing with organized tissue complexes (Richards and Kavanagh, 1947). In the case of unicellular organisms the use of total cell number of a uniform suspension seems a legitimate criterion of growth, assuming that the mean cellular size is constant, and an optimal cell density eliminates the possibility that the rate of division for a given cell may be influenced by the proximity of surrounding cells. Under conditions of optimal nutrition for colonies of simple unicellular organisms like yeast, the expected logarithmic progression in number of organisms with time has been obtained (Richards, 1928). The yardstick used to measure growth, namely the cell number, emphasizes the morphological finding in this case, that biological growth is fundamentally of the multiplicative type, cell division being the essential morphological event which determines cell number, and that each unit (cell) is an independent entity with the inherent capacity for growth.

This simple and direct type of mensuration also underlies measurement of size as a function of time for the cellular aggregates of metazoan organs and organisms. The fundamental observation that cell number does increase with time in a growing multicellular organism, supports the use of size as a criterion of growth, and enabled Minot (1908) to expound the conception of growth in terms of size and age, and bring it within the field of mathematical inquiry. In metazoan tissues, however, a cell is no longer an independent unit, and cellular redistribution and migration is just as much a factor in growth as actual multiplication. It is this essential consideration which led to the study of shape and form of growing cellular aggregates, and a quantitative expression of this aspect is embodied in the 'method of transformations', used by D'Arcy Thompson (1942). This method has been extended mathematically to express growth in terms of rate of change of shape (Medawar, 1947), but is only valid for homeomorphic shapes. This method of continuous parameter transformations cannot be applied to phases in development, with rapid changes in complexity, and other biological transformations, based on topology (Needham, 1936), and new embryological classifications (Woodger, 1947) have been introduced.

The interdependence of cells in multicellular organisms is to be seen not only in morphological analysis of growth *in vivo*, but finds expression in the quantitative aspect of growth of homogenous tissues grown *in vitro* under continuous agitation and optimum nutrition, to duplicate the conditions already noted, for a logarithmic progression in unicellular organisms. Fibroblasts grown in such circumstances (Harris, 1955) fail to give a logarithmic growth curve, and the specific velocity of growth progressively falls from the outset to a limiting value until the rate of cell multiplication balances the rate of cell death. Harris also found that the inoculum size for smaller inocula was of importance in initiating growth, and seemed to bear a relationship to the cell density; a single cell will only grow if the volume of the medium surrounding the cell is of capillary size. The interpretation of this observation as an isolated event is difficult, but it points to the deduction, substantiated by observation of the behaviour of cells *in vivo*, that growth in a complex cell aggregate cannot be simply interpreted in terms of size or cell number without taking into account the particular morphological and kinetic manifestations of growth for the particular tissue. Of paramount importance in this respect is the finding in most growing tissues that the initiation of growth, in both regenerative and ontogenetic types, involves migration or cell movement and not cell division (Medawar, 1947). The competence of a cell to migrate is intimately related to differential gradients in tension existing in a tissue aggregate, and also to qualitative characteristics of the surface properties of the environment, which are so ill understood but may be classified under a general term, the 'cellular environment'. Whilst it is impossible to simplify

these relationships with any degree of confidence, observations pertaining to regenerative growth allow for certain generalizations.

It is clear that cell migration underlies the kinetic tactics of regeneration in both epitheliocyte and many mechanocyte tissues taking part in wound healing. The locus of this phenomenon in epimorphic types of regeneration is identified with the immediate zone of host tissues bordering the zone of discontinuity established through injury. In morphyllaxis, and in blastemas recruited systemically, migration of cells plays a primary role in the growth process, and although it is convenient to differentiate between epimorphosis and morphyllaxis on morphological grounds, the difference is less clearcut from a kinetic standpoint. This largely relates to differences in gradients of migration and the capacity with which an organism can reorientate its individual units. It follows that the size of the regenerated structure loses much of its theoretical significance, in terms of cell number, and restitution is much more logically related to the capacity for a cell aggregate to change its shape or form than to restore its original weight or cell number. It is also apparent that the process of reorientation implicitly defines growth as directional, and in regenerative studies in wound healing it is clear that the axis of growth, with time, is identified to occur essentially at right angles to the zone of discontinuity. It is also clear that the mean cell density in a given tissue, for a particular set of environmental and metabolic conditions, is constant, and observations on the density of structures at the growing edge of a wound, healing under normal conditions of health, support this assumption. It follows that growth of a regenerate in wound healing, in which size and shape of the deficit is indeterminate, must be correlated with the *linear* rate of growth at right angles to the growing edge. It is also apparent that rate in change of size (volume) of a regenerate by itself is no criterion of rate of growth ; and that the rate of growth is intimately related to the surface area of the regenerate at a particular time. The uncritical measurements of regenerates in terms of volume or area have led to the entirely erroneous impressions of growth rates in wound healing. This particularly applies to the careful data of Young, Fisher, and Young (1941), from which they suggested that large wounds heal " faster " than small wounds ; that this assumption is not valid is clearly shown by recalculation of their data in terms of linear growth rate, which shows that the rate does not vary significantly with change in size. The mathematical analysis of growth curves for regenerates have also been based, largely, on measurements of size (Du Nouy, 1936 ; Fauré-Fremièt and Vlès, 1919 ; Robertson, 1923). Whilst it has been shown that no biological significance can be read into the *exact* analytical form of a curve of growth (Gray, 1929 ; Medawar, 1947), the objections are even more fundamental. It is clear that for regenerates of different shape, growing at equal linear rates of growth, the relationship of size with time may take any form. Thus, using a power series in the age of the given regenerate, any analytical function may be expressed (Backmann, 1938) as :—

$$W = a + a_1t_1 + a_2t_2^2 + \ldots$$

where W is the size (weight), t the time and $a, a_1, a_2 \ldots$ are constants. With change in shape of the regenerate a new set of parameters is required to express the form of the curve. This objection is particularly relevant to the practical documentation of data on wound healing, in which shape may vary with the exigencies of a particular experiment. The use of the linear growth rate, besides appealing on theoretical grounds, is essentially applicable to wounds and regenerates of any shape, and furthermore allows for the distinction between reduction due to true growth of a wound (with change in surface area) and distortion (change in size, without change in surface area).

The use of linear measurements in the documentation of growth data in wound healing has also been advocated by Henshaw and Meyer (1943) on other grounds, in respect to the regeneration of epithelium. It would appear that the original simple relationships determined by Lumiere (1917, 1918) for healing of wounds are most acceptable, both on theoretical and practical grounds. Lumiere's relationships—that the absolute rate of healing is constant and that the total time of cicatrization (healing) is approximately proportional to the greatest breadth of the wound—are essentially based on linear measurements of growth. In view of the kinetic picture of regeneration which the role of migration implies, it is difficult to rationalize the use of *specific growth rate* as a measure of regenerative growth, a usage which essentially draws attention to the multiplicative energy of the system (Medawar, 1947) as opposed to spatial redistribution. For this reason the experimental data to be presented only gives *absolute* measurements of linear growth rate for different aspects of regeneration in wound healing.

Method of Mensuration Adopted.—In the studies which follow, the types of regeneration show not only marked individual variations in growth rate but differential variations in rate along the growing front (isopleth). There are certain objections to the use of ' mass ' curves of growth, which, as Davenport (1934) has pointed out, may be corrupted to a sometimes incalculable extent by curves of distribution. Nevertheless it is considered legitimate to determine a mass curve of growth for a given aspect of regeneration, based on *mean* linear rates of growth along an individual isopleth, to facilitate prediction of events (for example in bio-assay studies) and to permit correlation and analysis on comparable premises of the different regenerative processes involved in healing of external wounds.

The change in size or area (Da) of the whole observable deficit is measured for finite time intervals, (Dt) of comparable magnitude for a given example, and sufficiently short to minimize fallacies relating to alterations in the axis of growth due to a large change in the length of the isopleth. The mean linear advance (Dl) in time Dt, is obtained by

$$Dl = \frac{2\ Da}{S_T + S_{T_1}}$$

where S_T and S_{T_1} are the total lengths of the isopleths at times $T = t$ and $T_1 = t + Dt$. The interval Dt is chosen to enable accuracy of measurement of the change in size by planimetry, and the length of the isopleths are measured as accurately as possible by a perimeter. Certain unavoidable errors arise in

connexion with measurement in specific problems which will be referred to in the appropriate sections, particularly relating to ear chamber measurements, in which the whole of the growing front may not be visible, and measurements are carried out on that portion of the blastema which is on view on the central table. In the types of regeneration studied —namely, growth of the repair blastema, contraction, and epithelial regeneration—the data obtained are plotted as a simple growth curve, in which the linear advance (Dl) is plotted against time (t) on a linear scale.

GRANULATION TISSUE

The growth of granulation tissue *per se*, plays an important part in the reduction of the spatial deficit in wound healing. In certain situations, for example, the organization of zones of tissue destruction in

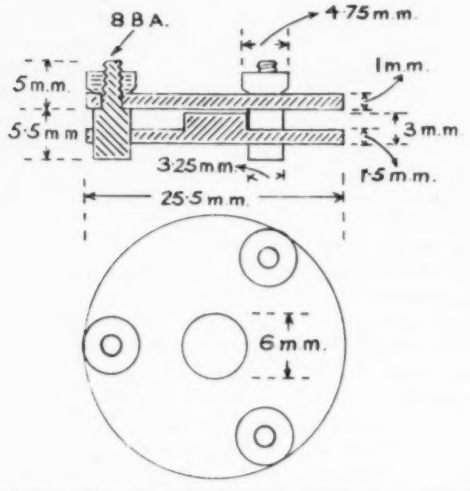


FIG. 628.—Plan of modified Sandison-Clark ear chamber drawn to scale, with measurements specified. The perspex ' cover-glass ' may be replaced with one constructed from mica and perspex for observations using higher magnifications.

rigid organs, where little if any contraction occurs, the young regenerate may consist entirely of granulation tissue which in turn may differentiate in various directions. The growth of the bony metaphysis, the transition of the ruptured ovarian follicle to a corpus albicans, and the absorption of fœtal structures (Meckel's cartilage, portions of the suprarenal cortex) are all basic physiological mechanisms closely related to the formation, growth, and differentiation of granulation tissue (Hadfield, 1951). The growth of granulation tissue may be accurately observed *in vivo* by means of the transparent-chamber techniques, using rabbit ear chambers (Sandison, 1928; Clark, Hitschler, Kirby-Smith, Rex, and Smith, 1931; Williams, 1954; Ebert, Florey, and Pullinger, 1939) and chambers in the dorsal skin fold of mice (Algire, 1943). Although qualitative studies have been carried out in detail, particularly by Sandison (1931) and Clark and Clark (1936), and measurements of the rate of growth at various points on the growing surfaces have been made, a growth curve for the entire tissues growing to completion has not been determined. The following experiments, using the rabbit ear chamber technique, have been undertaken to establish growth curves for granulation tissue growing into a rigid space.

Experiments.—Round-table ear chambers, of the Sandison-Clark pattern, were inserted into the ears of adult male rabbits. The animals used were of a long-eared semi-lop variety, of weight varying from 2–4 kg. Throughout the experiments the animals were kept in a constant temperature environment (70° F. ± 2° F.) and on a standard diet (Bruce and Parkes No. 18).

In most cases the animals had a chamber inserted in each ear, and only animals which registered a gain in weight over the period of observation are considered. Ears which showed the slightest sign of infection near the round table of the chamber are excluded from consideration.

Ear Chamber Design.—The chamber used throughout these experiments is shown in *Figs.* 628, 629. The entire chamber is made of perspex (methyl

FIG. 629.—Ear chamber in situ in rabbit's ear six months after insertion.

monacrylate), including all screws, pillars, nuts, base, and ' cover glass '. This construction was adopted, partly to eliminate excess weight, and partly to ensure freedom from local radiation scatter due to metallic components in investigating the effects of ionizing radiations (not included in the present study). The thick perspex cover-glass used did not allow for detailed studies using higher-power objectives, but ensured rigidity of the chamber and fixed dimensions of the tissue space. The impression has been gained that perspex causes less tissue reaction than mica, although this is apparently not conceded by Clark (1954). The tissue space is accurately fixed at 100 μ (except where otherwise stated), using graduated feeler gauges in the process of assembly. The round table is in every case 6 mm. in diameter. By adjusting the pillar setting to give the correct depth of space when assembling the chamber, and then fixing the pillars to the base with solvent (chloroform), the need for spacers, buffers, and washers is eliminated and the table surface is free from any mechanical obstructions to the growing tissue.

Technique of Insertion.—This differs only in detail from that described by Ebert and others (1939), and only certain aspects will be mentioned. The chambers are inserted under intravenous nembutal

anæsthesia, with full aseptic precautions, and using a 'no touch' technique. A topical application of penicillin powder is used at the time of insertion. Initially, parenteral penicillin cover was also instituted, but abandoned as unnecessary later. Since the rate of growth of new blood-vessels is considerably affected in favour of more rapid growth by the proximity of large blood-vessels (Clark and others, 1931), the site chosen in the present experiments is that portion of the ear midway between the middle artery and the peripheral vascular arcade, in order to obtain a more uniform vascular surround. This has probably prolonged the latent period somewhat, and gives lower average rates of growth on the whole than those obtained by Clark and Clark (1933 a, b), but is considered to be more representative of granulation tissue formation in normal circumstances. The insertion is made in either the cranial or caudal half of the ear, selection being based on the thickness of the cartilage. Owing to the table height being fixed (1·5 mm.), it is advisable to choose an area of cartilage which approximates to this thickness in order to ensure not only stability, but also to eliminate excess dead space and the attendant risk of infection. During the course of dissection of the skin-flaps, the use of a No. 18 Paragon blade is invaluable and far superior to a Graafe knife or a modified scalpel with a ground, rounded tip.

Initially, external splints were used to protect the cover-glass and ensure chamber stability. These were soon discarded as quite useless. Where slight scratches of the perspex cover, which sometimes occurs, were undesirable for any particular reason, a small shield cut from cleared, old photographic film, and indented at the edges to fit the chamfer of the nuts, was 'clipped' to the front of the chamber. Usually this precaution is not taken.

Subsequent Care and Measurement of Growth.—Photographic records of the whole table area (*Fig.* 630) are made every second day, excluding the latent period—that is to say, about the first 7 days, and excepting week-ends, when a 3-day interval elapses between photographs. The animal is photographed, unanæsthetized in a sitting posture, using a simply modified rabbit holder which imposes no undue restrictions on the animal. For photographing, the ear chamber is gently held on the horizontal stage of a vertical photomicrographic apparatus fitted with a ¼-plate bellows camera and a specially designed stage applicator (*Fig.* 631). Photographs are taken with full fixed bellows extension, using a 2-in. photomacrographic lens (unless otherwise stated), the focus being adjusted by the rack and pinion movement of the stage. A Pointolite source of illumination is used in conjunction with a Wratten dark green filter.

Subsequently the photographic negative is placed in an enlarger, and this is adjusted to superimpose the enlarged field on to a paper, which has a circle of 16 cm. diameter drawn on it, thus giving a magnification of 160/6 = 26 2/3 diameters. The limit of the growing edge is now traced on the paper as a contour line. The end point chosen for the growing edge is taken to be the outer edge of the hæmorrhagic zone, which forms in advance of the capillary loops. For each chamber, successive tracings are made on the same paper, thus giving a series of isopleths.

The isopleth tracing is now transferred to a drawing-board, and area measurements of the

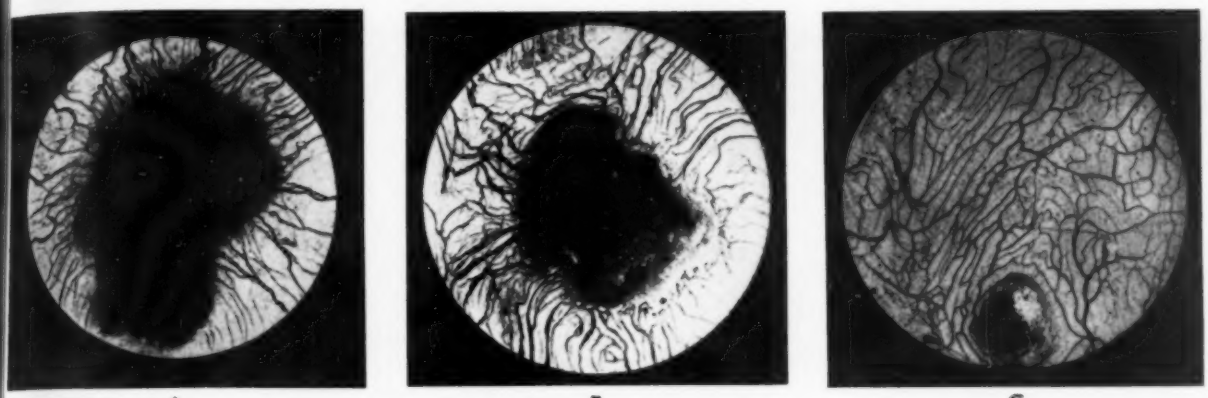


FIG. 630.—Photographs of the entire table area in three different chambers at various times after insertion: A, Chamber 23L, 14 days. B, Chamber 20L, 27 days. C, Chamber 16L, 35 days. (Approximately × 7·5.)

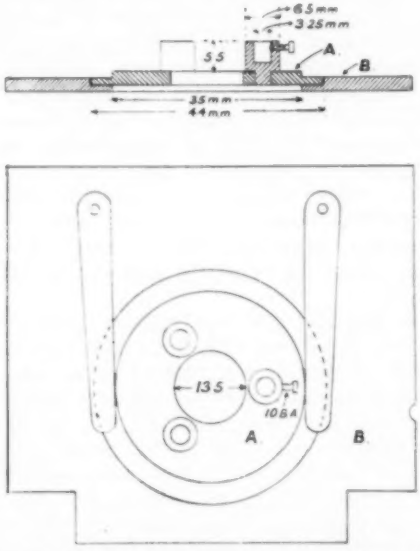


FIG. 631.—Plan of stage applicator used in conjunction with the ear chamber modification illustrated in *Figs.* 628 and 629.

segments between successive isopleths are made with a planimeter, and the length of each isopleth is measured with a perimeter. Using the appropriate reduction factor, the linear advance of the growing front for corresponding intervals of time is calculated. During the early stages of growth the table area may be eccentrically placed in reference to the growing tissue front, so that growth appears unequally on the

FIG. 632.—Typical isopleth charts for three individual chambers growing to completion. (Note.—The time intervals between successive isopleths, illustrated in a given chart, are not equal.)

table area. This may also be due to an earlier appearance of growth on the table, which inherently grows at the fastest rate, owing to the differential intravascular pressures which exist (*see below*). In measuring the visible portion of the blastema only, these factors must be borne in mind. However, such peculiarities may be correlated with quantitative findings in chambers which give a very uniform concentric type of growth. This has been done, and with certain reservations the mass curve of growth can still be quite satisfactorily interpreted.

Additional Experiments.—In addition to the measurement of growth to completion in 100-μ chambers, some chambers using spaces of 50 μ and 200 μ were studied in a similar way. Also some chambers were constructed with a wedge-shaped space tapering off to nothing from a maximum thickness of 150 μ and the growth curve determined.

A few round-table transparent chambers were inserted into the dorsal skin-flaps of albino mice, and the growth of granulation tissue studied in a similar way. Here, however, only the initial growth into the space was studied owing to infection developing in the later stages (after the fourth week) of growth. The results in mice chambers were quantitatively less satisfactory owing to poorer stability of the chamber, and drifting of the tissues.

More detailed and essentially qualitative morphological studies were made in selected ear chambers in rabbits using higher powers of magnification, particularly in searching for mitotic figures in vascular endothelium, and loops, and to observe the behaviour of endothelial nuclei in the growing components of the vasculature.

RESULTS AND CONCLUSIONS

1. Quantitative Findings.—

a. Latent Period.—The average latent period before growth first appeared on the table was 8·2 ($\pm$ 1·2) days in a series of 80 chambers. The latent period found for growth of the blastema in Sandison-Clark ear chambers is much longer than the true value, and depends a great deal on the amount of damage at operation and the distance between the first vascular loops which form and the table edge. Also the rate of growth of the blastema depends to a large extent on its proximity to afferent vessels and their size. In this respect another observation is cogent; if the regenerate formed in an ear chamber is partially or totally destroyed, regeneration often has been found to recommence within 24 hours, suggesting a very short latent period. The shorter period of vascular formation which accompanies epithelial regeneration (*see below*) is also suggestive. Sometimes, if a chamber is inserted adjacent to the central artery, a very short latent period is obtained. However, it is considered that the ear chamber technique allows little to be deduced in respect to latent period, and the influence of factors on the latent period known to alter the rate of growth of the blastema—for example, temperature. However, it seems clear that the latent period is considerably less than seven days, and possibly as short as 24 hours. This is substantiated by observations on the reconstitution of vascular beds determined by the method of quantitative morphological analysis of Chalkley (1943) in mouse chambers, by Chalkley, Algire, and Morris (1946); vascularization occurs by a process which differs from endothelial budding and probably also takes place initially as part of the demolition phase in ear chambers prior to the establishment and growth of the blastema.

b. Curves of Growth.—The types of isopleth chart obtained are illustrated by examples in *Fig.* 632. Individual curves of growth for selected chambers are shown in *Fig.* 633. *Fig.* 634 shows the 'mass' curve for absolute linear growth, in 12 chambers. The mean rates of growth obtained in a series of 80 chambers, in which a linear relationship was obtained for the initial growth over at least 50 per cent of the total table area, is set out in *Fig.* 635; the majority of these chambers were used for the study of agents which modify growth rate (e.g., ionizing radiations) and the rates of growth represent the normal control period prior to exhibition of the agent. It also includes 8 chambers, in which the chamber became infected at a late stage, but the portion of the growth curve used, represents growth free from infection; the latter is readily detected by

a quantitative alteration in the rate of growth and qualitative changes in the regenerate due to inflammation, namely vascular changes and abnormal cellular infiltration.

A study of the isopleth charts and the graphs clearly indicates that the rate of growth in individual chambers shows considerable variations along the tissue front, whilst the mean rate of growth for individual regenerates is also subject to considerable variation. However the growth curve for an individual regenerate growing to completion is essentially a linear relationship. The total time taken for a chamber to grow to completion is largely determined by the uniformity of the growth in reaching the table edges, and bears less relationship to the true growth rate.

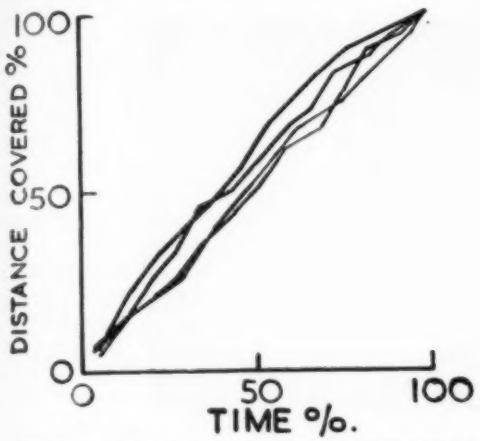


FIG. 633.—Individual growth curves for the repair blastema growing to completion in 4 ear chambers expressed as the percentage linear advance with time. The examples chosen represent the average range in departure from linearity encountered.

The 'mass' curve of growth shows a slight progressive departure from linearity throughout the total observation time which is significant, although no significant departure from linearity is observed in selected individual chambers (*see Figs.* 633, 634). It is considered that the slow fall off in rate in the mass curve represents a gradual reduction in the intravascular pressure of the terminal budding arcade, with time, as the distance from the parent vascular surround increases. That the proximity of afferent vessels and their size markedly affects the rate of growth of a regenerate or portion of a regenerate is clearly indicated by :—

i. The higher rates of growth obtained on that portion of the chamber proximal to the base of the ear and large vessels.

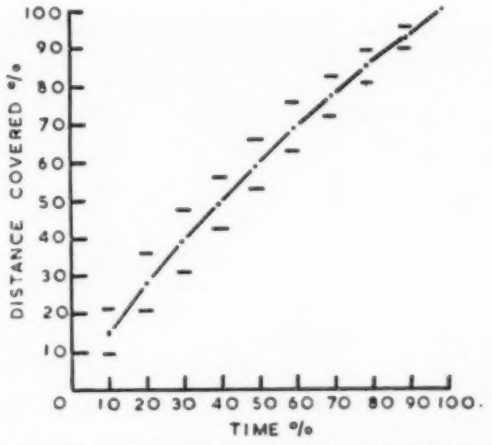


FIG. 634.—The 'mass' curve of the absolute linear rate of growth, for the repair blastema growing to completion in 12 ear chambers.

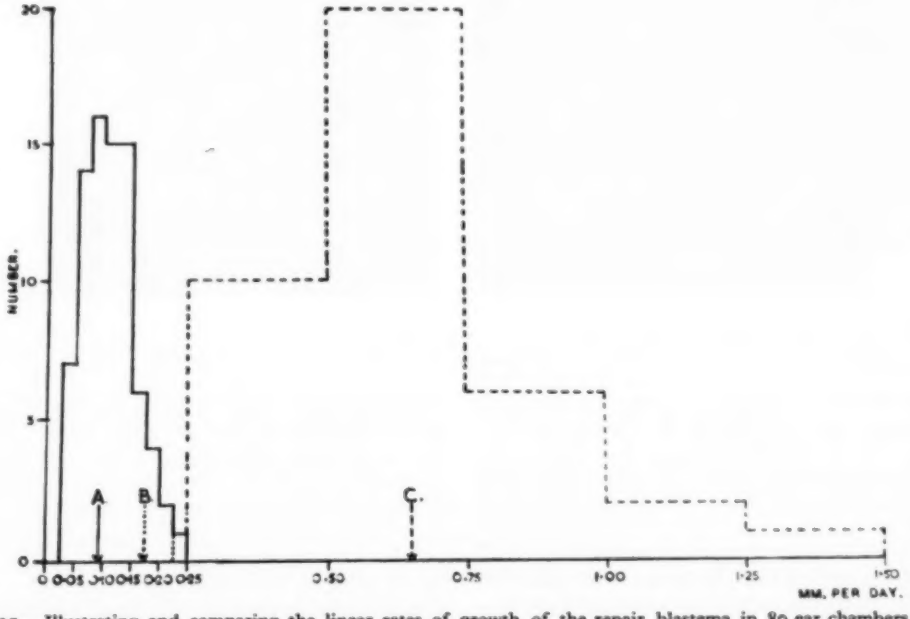


FIG. 635.—Illustrating and comparing the linear rates of growth of the repair blastema in 80 ear chambers (continuous line) with the linear rate of contraction in 40 flank wounds in the rabbit (broken line). The three arrows indicate the mean linear growth rates obtained for (i) the repair blastema in ear chambers (80 observations, continuous line A), (ii) epithelial regeneration under perspex cover in rabbits' ears (12 observations, dotted line B), (iii) contraction in exposed flank wounds in the rabbit (40 observations, broken line C).

ii. Higher rates of growth in a chamber with a substantial vascular surround, for example adjacent to the central artery.

iii. The transient increase in rate of growth which attends inflammation of a chamber before actual free pus is present.

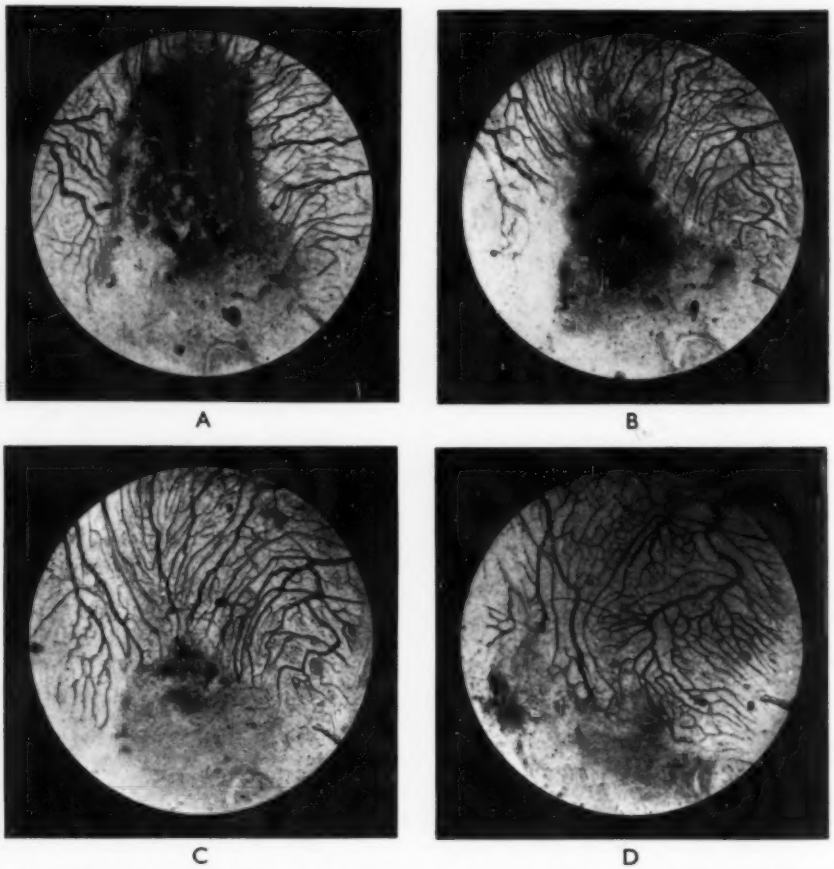


FIG. 636.—Illustrating growth of the blastema into ear chamber (7RA) with tissue space tapering from 100 μ to 'nothing'; (A, 15 days after insertion; B, 22 days; C, 27 days; D, 57 days). (Approximately × 7·5.)

The morphological pattern of granulation tissue growth in wounds can be related to similar factors. Another factor which could account for fall off in growth rate for certain chambers is drifting of the chamber in the ear with time. Whilst this was a feature of early Sandison Clark chambers (Clark and Clark, 1933) it is negligible in the Oxford modification (Ebert and others, 1939). Studies of vascular patterns, together with measurements of the chamber position in the ear with time using the present modification, fail to demonstrate significant drifting. It is doubtful, on theoretical grounds, whether minor migrations of the chamber do significantly alter mean linear growth rates in epimorphic regeneration into a relatively firm clot, even if slight distortion and differential alterations in pressure occur along the isopleth. The present quantitative studies, correlated with the qualitative behaviour of the growing front, fail to incriminate chamber drift as a factor invalidating this technique in quantitative studies satisfactorily conducted.

The data usually given for the rate of growth of blood-vessels, 0·2–0·6 mm. per day, is that of Clark and Clark (1933). This is much higher than that obtained in the present experiments, which have been conducted at comparable temperatures and conditions. It is probable that the figures of Clark and Clark represent selected optimal rates for isolated capillary buds, although the methods of measurement and calculation employed have not been made clear. The much lower values obtained for *mean* rates of growth in the determinations made here takes into account cessation or slow progress of growth which may occur along a portion of the front, by including this portion of the isopleth in a given calculation. Also, the positioning of the table at operation, farther away from the central arterial pedicle of the ear, lowers the average rates of growth of the regenerates.

A few experiments which were carried out with very thick chamber spaces (200 μ) failed to demonstrate significant changes in growth rate from 100-μ chambers; the thickness of the vascular growth and the density of the advancing hæmorrhagic zone make measurement with any confidence very difficult. Experience with 50-μ chambers has been disappointing; it has been found that growth often ceases spontaneously despite apparently normal conditions. Initially it was thought that warping and shrinkage of the tissue space had occurred. However, removal of the chambers and remeasurement of the tissue space failed to confirm this suspicion, and the

mechanical construction of the chamber makes this change almost impossible. In the literature many illustrations of tissue fields, with other chamber designs, depict tissues of a thickness and density which greatly exceed those obtained with depths of tissue space specified in the legends. It is suggested that either the buffer size is difficult to calibrate in some chambers, or the mica cover-slip stretched over the buffers becomes convex upwards with an increase in the central thickness.

The rate of growth which takes place in a wedge-shaped tissue space is illustrated in *Figs.* 636, 637; a fall-off in growth rate occurs rather abruptly although evenly. This observation is difficult to interpret, although it suggests that a simple mechanical explanation is more feasible than a chemical one. The observations which have been made on the rates of growth for this type of regenerate, of varying definitive sizes, fail to indicate that changing local metabolic factors bring about slowing and finally cessation of growth, as regeneration approaches completion. Robertson (1923) and Fauré-Fremièt and Vlès (1919) have arrived at a hypothesis that the rate of growth in regeneration is quantitatively related to an equilibrium state defined by an auto-

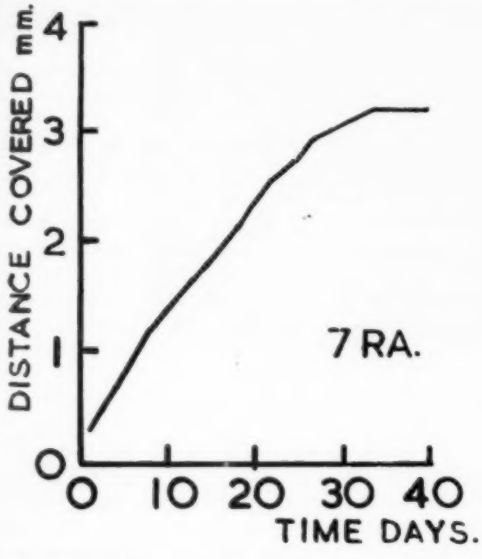


FIG. 637.—Growth curve for chamber 7RA, with wedge-shaped tissue space (*see Fig.* 636).

catalytic reaction in which the inhibitory factor is related to an exhaustion of reagents. This view has been modified by Needham (1952), in that an active inhibitor is postulated, which is in some way related to definitive size of the regenerate. The fallacies which are implicit in the use of size as a means of mensuration in growth, have been discussed, and observations made on the linear growth rates for regenerates of varying definitive sizes fail to support the reality of a simple physicochemical exposition of regeneration in these terms.

2. **Qualitative Findings.**—Detailed cellular studies of growth in ear chambers have been made by Sandison, the Clarks, and their associates (*see* Williams, 1954, for reviews of literature), and in this country by Sanders, Ebert, and Florey (1940) (*see* Florey, 1954, for composite accounts). Attention will be drawn to certain aspects only, which apply more strictly to the interpretation of quantitative data.

a. Capillary Bud Formation.—The solid elongated endothelial protrusions which grow out from the terminal vascular arcades bordering the zone of

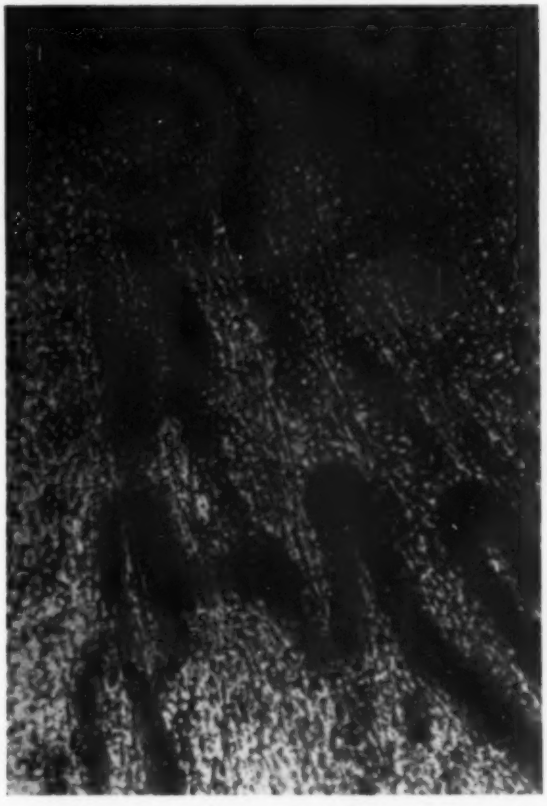
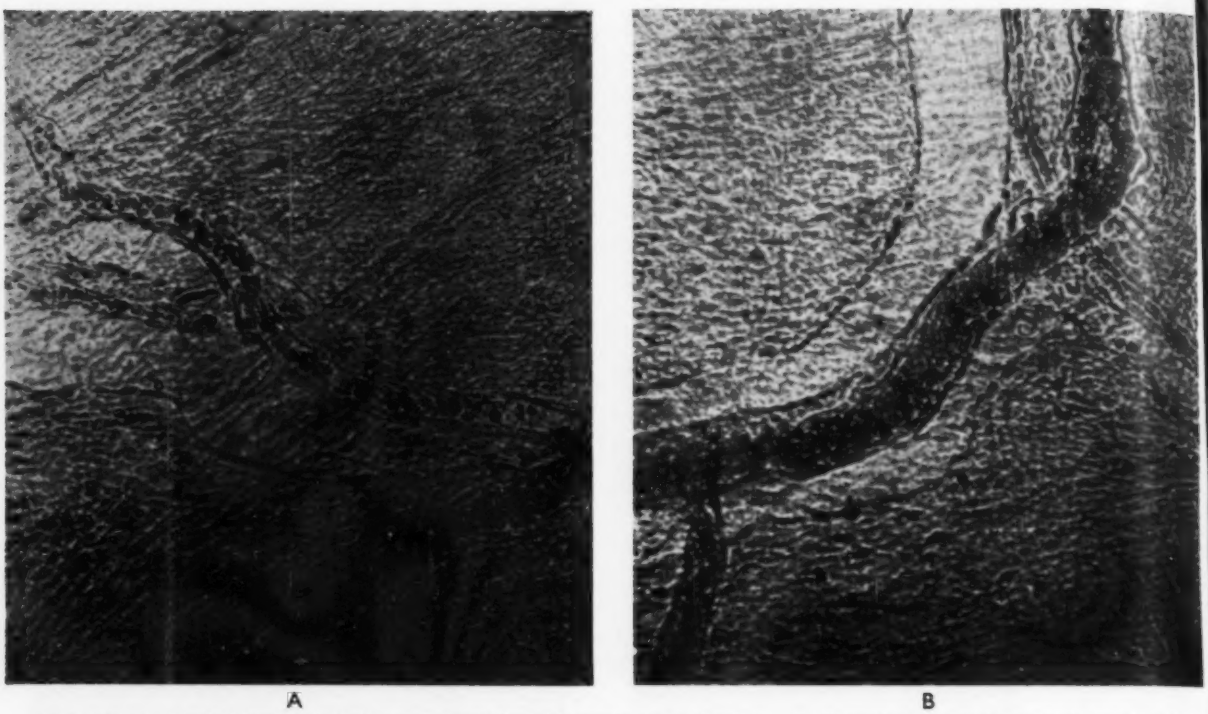


FIG. 638.—Four typical elongated capillary buds, growing out from terminal vascular arcade into unorganized zone. The solid endothelial protrusion consists of a peripheral ectoplasm, which may or may not contain endothelial nuclei in syncytial formation. The centre of the bud contains a core of red blood-cells, and leucocytes, which freely penetrate the bud and pass into the unorganized zone as an advance 'hæmorrhagic' formation, to be in turn organized by newly forming buds and macrophages. (Thick chamber, 120 μ; × 100.)

discontinuity (*Fig.* 638), are essentially directed at right angles to the growing front and always grow directionally towards the zone of discontinuity. The bud protrusion initially consists of a solid cytoplasmic process with a peripheral zone of nuclei arranged as a syncytium. The bud, which later becomes hollowed out, is freely permeable to blood-corpuscles, which penetrate the length of the bud to form a profuse hæmorrhagic zone in advance of the growing buds (*Figs.* 630, 638).

Prolonged observations of these buds have been carried out in order to determine the behaviour of the endothelial nuclei. Mitosis has never been observed to occur in the buds, in the vascular endothelium of the formed regenerate, or in regenerated lymphatic buds and capillaries (*Fig.* 639). Sanders (personal communications) also has failed to observe mitosis in capillary buds, although Clark and Clark (1933, 1939) have reported seeing mitosis in capillary buds without presenting photographic



A B

FIG. 639.—A, Typical lymphatic bud, growing out alongside venule in ear chamber. B, Formed regenerated lymphatic trunk and branches alongside arteriole and venule in the completed regenerate of an ear chamber. (Electronic flash photograph ; × 200.)

FIG. 640.—Showing the distribution of fibrous tissue surrounding an arteriole and venule in an ear chamber which was irradiated four months previous with a single tissue dose of 1000 r (γ) rays. The photograph has been taken with polarized light, and the amount of fibrous tissue present is not greatly in excess of normal. Whilst there is a tendency for some fibres to differentiate parallel to the vessels, particularly arterioles, there is no relationship between the direction of the fibres and the path of the vessels, suggesting that direct mechanical distortion results in the vascular bed, due to fibre formation. (Polarized light ; × 200.)

records. In the illustrations in Lewis's paper (1931) of vascular tissue grown *in vitro*, there are also few mitoses to be seen in endothelium, but attention is drawn to the active migration of the tissue as shown by the appearance that " the capillaries were pulled along by solid amœboid growing tips ". However, observations of growing capillary buds and loops clearly demonstrate the extreme lability with which endothelial cytoplasm migrates and the mobility of nuclei in the cytoplasm ; one nucleus can be observed to pass another both in the endoplasm of the bud and the endothelial wall of blood-vessels. The same lability is seen in remodelling of the vascular bed which occurs with ageing, Clark and Clark (1939), disappearance of ' effete ' capillaries, in which blood-flow has ceased for 24 hours or more, being affected by ' retraction ' or migration of endothelium back into functioning parent vessels, and not by degeneration of vessels in situ or metaplasia into other mechanocyte tissues, for example fibroblasts.

The inference to be drawn from these observations is threefold :—

1. The facility with which vascular endothelium can migrate is absolutely established by direct observation.

2. There is a remarkable conservation of formed vascular endothelium in the process of both new capillary formation and in vascular remodelling, both *in vitro* (Lewis, 1931) and *in vivo*, and endothelium behaves as a strictly independent tissue, which maintains its status, and only arises from pre-existing endothelium in regenerative processes ; also vascular and lymphatic endothelium are clearly independent in regeneration (Clark and Clark, 1932–6).

3. The paucity of observable mitoses in endothelium either means that it rarely occurs in the very

rapidly growing regenerate, or that mitosis is extremely rapid, and usually evades identification.

The latter supposition is quite reasonable, when it is related to the paucity of observable mitoses in other actively growing mechanocyte tissues, for example cartilage cells in the plate columns of a growing bone. Finally despite fundamental biological objections the possibility that amitotic division occurs cannot be excluded. However it is clear that the tactics of vascular regeneration is primarily one of migration, and this fact must be borne in mind in the interpretation of quantitative data.

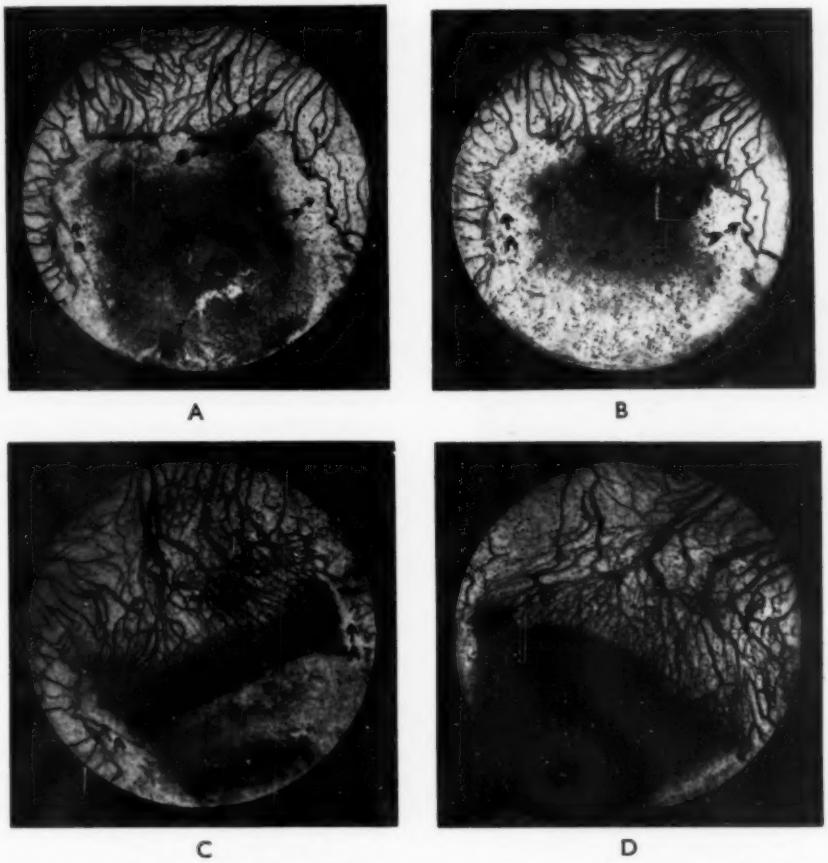


FIG. 641.—Chamber 40L. A, 18 days after irradiation (single tissue dose, 3000 r (γ) rays). Cessation of vascular growth occurred immediately after irradiation, with disappearance of the advance 'hæmorrhagic' zone and capillary buds, and resulting in a clear area (A) consisting partly of a viable connective tissue, which grows out slowly beyond the vascular component. At (B) a small focus of normal free budding has been induced by trauma. B, 27 days after irradiation. Vascular regeneration is entirely confined to point (B) and is radiating outwards, both into the unorganized 'old' clot, and into zone (A). C and D, Later stages at 41 days and 48 days respectively. Note the advance zone of new 'hæmorrhage', and the progressive organization of connective tissue zone (A) entirely by vessels which have grown out from (B). (× 7·5.)

b. Regeneration of other Mechanocyte Tissues.—The regeneration of fibroblasts and differentiation of connective tissues has been thoroughly studied in ear chambers by Stearns (1939, 1940 a). Active migration of fibroblasts occurs in advance of the growing vascular buds, into the hæmorrhagic zone, together with macrophages and small round cells. Initially the fibroblasts exist as stellate or bipolar cells, orientated irregularly, but with the regeneration of vessels, they tend to become alined parallel to the vessels. The directional migration of fibroblasts into the unabsorbed clot is apparently facilitated by a stereotropic phenomenon, probably allied to thigmotaxis in epithelial regeneration, in which the threads of the fibrin in the clot act as surfaces for the temporary attachment of fibroblasts during migration. However, the development of fibre in the regenerate is not related to fibrin but depends on the presence of fibroblasts, and develops extracellularly. Fibres usually form 7–10 days after vascular growth has already commenced and are at first orientated parallel to the line of the vessels, in accordance with the orientation of the fibroblasts. However, the final pattern is determined by the direction and magnitude of the local tensions existing in the tissue.

Primarily, the fibre pattern which is seen in a particular regenerate at a given time is the morphological expression of differential mechanical tensions which exist at that time, and is subject to dynamic change with alterations in the tissue tensions. Observations on regenerates in chambers with ageing over a period of months fail to suggest that the development of fibre *per se* causes distortion of the regenerate. Despite the presence of mature fibres, even of a magnitude seen in irradiated chambers (*Fig.* 640), there is little evidence that the vascular pattern alters as a result of direct distortion or contraction. However, in the presence of a suitable stimulus, extensive remodelling of the entire vascular and

lymphatic bed can occur with great lability, even in a so-called mature regenerate of many months' standing, a process accompanied by extensive modifications in the fibre pattern. It must be borne in mind that the vascular pattern in mature regenerates, with extensive fibre development throughout, bears little relationship to the lines of

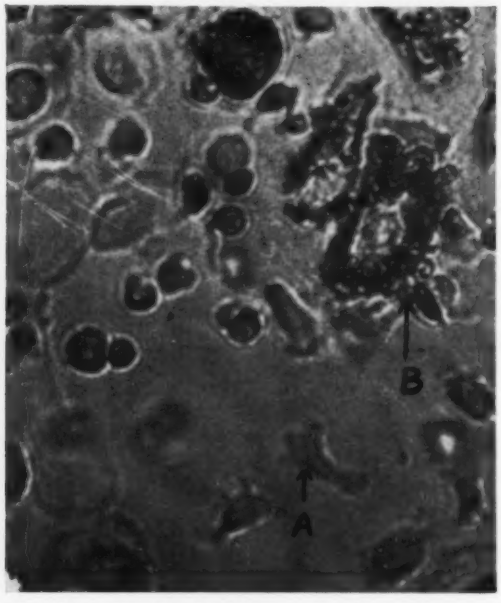


FIG. 642.—Showing the advance migration of cells into the unorganized zone in an ear chamber (A, lymphocyte with pseudopodia; B, macrophage with ingested red blood-cells). (Electronic flash photograph; × 400.)

mechanical tension, in contrast to the orientation of the connective tissues. In both preformed and regenerated ear chambers, the portion of the regenerate under view on the table shows very little evidence of fluctuation in size with maturation and fibre development, for periods of time which may occupy months after completion of regeneration. Whilst collagen change in connective tissue and shortening occurs over the years, with ageing, it is very doubtful if this is a significant factor in providing a passive mechanism for closure of wounds with tissue loss during the period following injury until primary spatial restitution is completed. In ear chambers, with the differentiation of connective tissue fibres, one would expect to observe progressive distortion of the regenerate, and 'pulling' of outside tissues on to the centre table, over the period when contraction in wounds is known to take place. This has not been observed to occur. The fact that the chamber imposes conditions of rigidity on the tissues must, of course, be taken into account. However, the lability with which cells migrate in the chamber, and the modification of fibre patterns by local alterations in tissue tension, suggest that should a passive mechanical force of sufficient magnitude exist it would be capable of expression.

Whilst connective tissue fibre development permits extensive remodelling of vascular beds by endothelial migration, it does modify vascular growth by bud formation. If a temporary differential depression of vascular regeneration is evoked, for example, by ionizing radiations, without repression of connective tissue development, a zone of mature viable connective tissue may precede the line of the vessels. In such circumstances, when vascular regeneration recovers, normal bud formation with hæmorrhage does not occur, but slow regeneration by looping and abnormal budding takes place (van den Brenk, 1955). If an area of hæmorrhage and tissue destruction is induced by local trauma, active normal bud formation with hæmorrhage occurs into the zone of discontinuity and 'absorption' of the fibrous tissue, which previously inhibited normal vascular regeneration, may take place (*Fig.* 641). This observation seems to indicate that the formation of granulation tissue in wound healing provides a surface which is not only highly resistant as a barrier to infection and chemical permeation with substances like alcohol (Billroth, 1865; Melchior and Rosenthal, 1920) but acts as an aggressive agent for digestion of the dead tissues of the scab, and even enables absorption of a connective tissue matrix in living tissues (*see below*). For similar reasons, the appearance of granulation tissue is accompanied by the disappearance of fibrin (Arey, 1936).

The active migration of macrophages and small round cells (*Fig.* 642), which takes place in advance of the capillary buds and into the recently formed regenerate, can be observed in ear chambers. Ebert and Florey (1939) have demonstrated in ear chambers, by intravital staining, that monocytes of the circulating blood leave the vessels and change into freely moving macrophages and also into 'fixed' tissue phagocytes or histocytes, to be orientated along newly formed blood-vessels. The fact that certain cellular constituents of the mammalian repair blastema arise by systemic recruitment is of general biological interest, in that systemic migration and recruitment appears to be the sole source of the blastema for the epimorphic components of regeneration in certain lower organisms, for example, planarians (Wolff and Dubois, 1947).

WOUND CONTRACTION

The fact that 'contraction' plays a very important part in the spatial reduction of the deficit in wounds with tissue loss has been recognized for a long time. Spallanzani (1787) studied contraction of wounds in salamanders. Later Minervini (1904) recognized that contraction was one of the identifiable mechanisms which brought about spatial restitution in wounds with tissue loss, but he did not investigate quantitative aspects of the processes involved, and concentrated on the histological aspects of wound healing. Most of the studies on wound contraction have been carried out by Carrel and Du Nouy (Carrel, 1910, 1912, 1921, 1923, 1924, 1930; Carrel and Baker, 1926; Carrel and Ebeling, 1923, 1926; Carrel and Hartmann, 1916; Carrel and Du Nouy, 1921; Du Nouy, 1936). A quantitative analysis of the process has been difficult to interpret, owing to the use of area as a criterion for mensuration, for reasons already discussed. It was considered useful to repeat simple experiments of the type used by Carrel and Du Nouy (Du Nouy, 1936) and later by Young and others (1941) in order to follow the contraction of standard circular flank wounds with tissue loss, in animals.

EXPERIMENTS

Circular wounds were made in the flank of adult rabbits. The animals were anæsthetized with intravenous nembutal, the hair closely clipped and cleansed. A circular punch of known diameter varying from 1·2 to 3·0 cm. was then carefully used to make an impression on the skin, the latter being kept lax and unstretched during the making of the impression. The circle of skin and underlying *panniculus carnosus* muscle was carefully removed with a scalpel and curved scissors, particular care being taken to cut these tissues perpendicular to the surface. Ties for bleeding vessels were avoided if possible, hæmostasis being effected by simple pressure or by clipping the bleeding point with a fine hæmostat, leaving on for a while and then releasing. At no time is a cautery used to arrest hæmorrhage. The wound is smeared with a little penicillin cream, left exposed and allowed to heal. Under these circumstances less than 2 per cent of wounds become infected, and if this occurs the animal is excluded from consideration.

Every second day after operation, the wound is examined and photographed using a 35 mm. Exakta camera, with the appropriate extension tubes in place for a close working distance and to give accurate focusing. During photography, a thin perspex square etched with a 0·5 cm. grid ruling is held in light contact with the wound, to enable enlargement of the negatives to a fixed size for the purposes of tracing the wound edges on paper and mensuration by planimeter and perimeter. In this way the wound area and perimeter are measured and the average radius obtained is used as a measurement of mean dimensions for wounds approximating to a circular shape. The measurement of the mean linear rate of contraction in this way has been found much more accurate and satisfactory than that obtained by direct estimation of one or more diameters by rule or callipers, as used by Henshaw and Meyer (1943). Initially the wound edge was marked at operation by silver nitrate solution, but this gives less accurate determination of the original edge than the hair follicle pattern in the intact skin surrounding the wound. In all the measurements of wound size, the scab is left absolutely undisturbed throughout and no attempts are made to measure 'healing under a scab' as in Nettleship's (1943) determinations, which measure not only contraction of the original edge but also apparently endeavour to determine the extent of epithelial ingrowth. The continuous removal of a scab for purposes of measurement cannot give a true record of normal healing by contraction. It has been found that the scab in exposed wounds, by and large reduces in size, *pari passu*, with contraction. Any epithelium which is hidden by the scab consists of new regenerated epithelium, devoid of hair follicles and less pigmented and clearly different from the original epithelium of the wound margins. The scab usually remains lightly attached to this new epithelium but is never attached to the old epithelium with the progress of contraction—in such cases the free overhanging edges of the scab, which tends to become elevated as contraction also occurs in the base of the wound, are trimmed to reveal the true wound margin (*Fig.* 643). In most cases the growth of hair on the original skin needs to be clipped often to expose the wound.

Most measurements have been carried out on 1·2 cm. diameter wounds in rabbit flanks. Essentially similar experiments have been performed on rats (Glaxo hooded strain), using the midline of the back for the wound site. In one group of rats the edge and base of the wound, after surgical excision of the area in the integument, were uniformly cauterized with a dull red electrically heated iron, and the healing compared with that in identical uncauterized wounds. A large series of flank wounds in rabbits has also been studied quantitatively, following the administration of local ionizing radiations and cortisone, and forms the subject for separate communications.

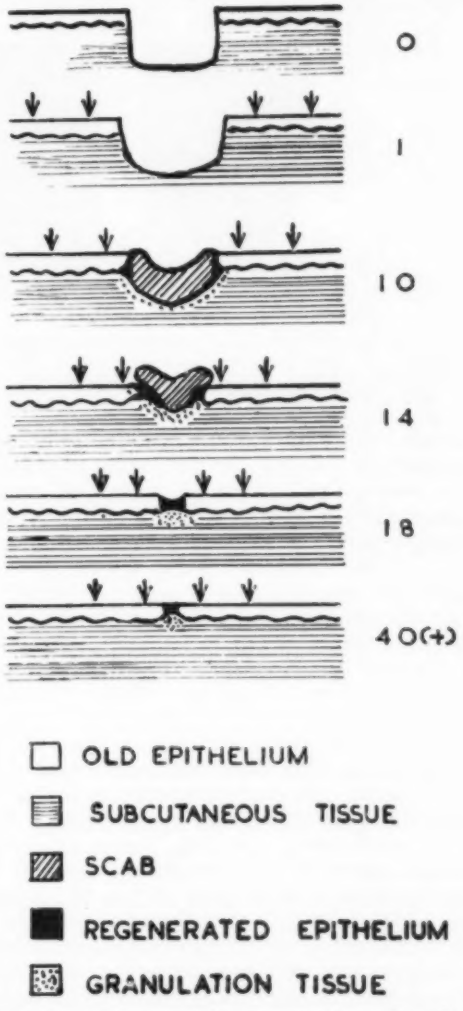


FIG. 643.—Diagrammatic representation of a healing exposed flank wound in the skin of a rabbit; *see text* for descriptions. The arrows represent fixed markers on the skin adjacent to the wound margin; the figures on the right of diagram gives the average time in days, after operation, for a wound of approximately 1·25 cm. in diameter.

RESULTS AND CONCLUSIONS

Description of Contraction in Skin Wounds.—In *Fig.* 643, the process of closure of a wound with tissue loss in the integument is represented diagrammatically. *Fig.* 644 illustrates the actual

appearances of a wound healing under the conditions of the experiment.

It is emphasized that contraction must be clearly differentiated from the epimorphic regeneration of new epithelium and granulation tissue which takes place simultaneously. The observation that contraction occurred at a time when granulation tissue also formed led Carrel to use the term 'granulous contraction' to define the process, thereby implying that contraction is due to the formation of granulation tissue, a view which has gained considerable support.

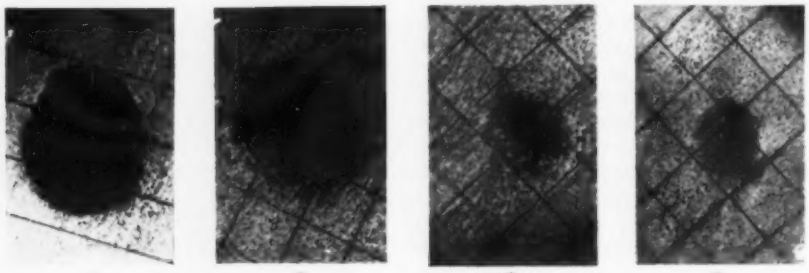


FIG. 644.—Photographs of a flank wound (68R) at specified times after operation, showing process of contraction. A, 6 days; B, 13 days; C, 15 days; D, 20 days. Etched perspex grid is superimposed on the wound. Note the old epithelial edge defined by the hair follicles and growing hair. In D the scab has been spontaneously sequestrated, revealing the residual central zone of regenerated epithelium. (× 1·5.)

Immediately following operation, the wound on the average becomes slightly larger, the edges are mobile and the shape is easily distorted. Within two days, the wound surfaces have dried and a hard scab has formed, attached firmly to the edges, which stabilizes the size and shape and prevents distortion unless the scab is fractured by quite intense manual pressure. The rim of tissues which surround the scab in non-infected wounds for about 1·0 mm. to 1·5 mm. are firm, but show minor signs of redness and congestion. Beyond this zone the skin is perfectly mobile and the entire wound also moves relatively freely on the lumbar musculature. During the next 8 to 10 days, very little change in size of the wound takes place, but towards the end of this period the edges of the scab slightly loosen from the skin margins of the wound. At this stage a sudden rapid progressive decrease in wound size occurs, the scab becoming progressively loosened and overhanging the wound margins, and gradually becoming raised in its entirety. The central portion still remains attached to the wound and, if detached, reveals a bleeding granulation tissue surface, partially covered at the periphery by new regenerated epithelium. When the contraction process ceases with shedding of the remaining scab, a small central area of regenerated epithelium is revealed, the size of which averages 1·5 mm. in radius in a wound of initial average size 6·33 mm. radius. In other words, contraction has accounted for approximately 70 per cent of the reduction in size of this type of wound, allowing for the decrease in size attributable to desiccation of the scab (*see below*).

Another feature of wound healing to which Carrel and Du Nouy (Du Nouy, 1936) drew attention pertains to changes in the skin and cicatrix, following complete closure. The central small area of the original wound which is covered by new regenerated epithelium progressively shrinks until it can hardly be detected in 1 to 2 cm. diameter flank wounds in rabbits. Over this period, which lasts a considerable time (several weeks to months), the original skin surrounding the central regenerate 'expands' back to about the original position. This change is represented diagrammatically in *Fig.* 644, and can be studied by drawing spaced concentric rings on the skin around the wound with silver nitrate, or by tattooing. It is rather significant that during the phase of rapid contraction concentric rings on the skin around the wound margin tend to approximate; if contraction is due to a passive shortening of collagen, with dehydration, in the thin firm zone immediately bordering the wound, one would expect an opposite result. It must also be noted that observations on ear chambers show that collagen fibres are initially orientated at right angles to the zone of discontinuity, parallel to the vessels of the granulation tissue, but continuous with and anchored to the mature tissues of the organism; in such circumstances, collagen shortening would tend to keep the wound open, rather than lead to contraction. The circular distribution of collagen occurs at a much later stage and after considerable maturation of the regenerate has taken place with differentiation of both arterioles and veins.

QUANTITATIVE ASPECTS OF CONTRACTION

In *Fig.* 645 growth curves for contraction of a series of 10 selected individual wounds made with a 1·2 cm. diameter punch impression are represented graphically; the absolute linear rate of growth is plotted against time. *Fig.* 646 shows the average growth curve for a series of 40 consecutive wounds. Attention will be drawn to certain relevant quantitative aspects of the process of contraction.

1. Initial Size of Wound.—It is impossible to make a wound in the skin of a fixed size surgically, owing to elastic retraction or contraction of the skin. On the average, it is seen that a definitive wound of 6 mm. radius retracts to a radius of 6·63 mm. At 24 hours a definitive size is stabilized with drying of the wound surfaces and initial formation of the scab.

2. Latent Period.—Prior to the onset of contraction the average latent period for 40 wounds was found to be 9·4 (± 2·3) days. During this time the average decrease in radius of the wound was 0·6 mm. This decrease in size is probably due to desiccation of the scab. It is noted that the latent period for

contraction is considerably longer than that for the formation of granulation tissue, but is considerably shorter than the latent period which precedes the differentiation of connective tissue fibre in ear chambers in rabbits (*see below*).

3. Contraction Phase.—This occurs precipitantly and progresses at a rapid linear rate, which varies from wound to wound, but in a series of 40 wounds averaged 0·65 (± 0·25) mm. per day. In *Fig.* 635 these data are presented and compared with the rates of growth of granulation tissue in 80 Sandison Clark chambers, inserted in a field much more vascular than the rabbit's flank. The large

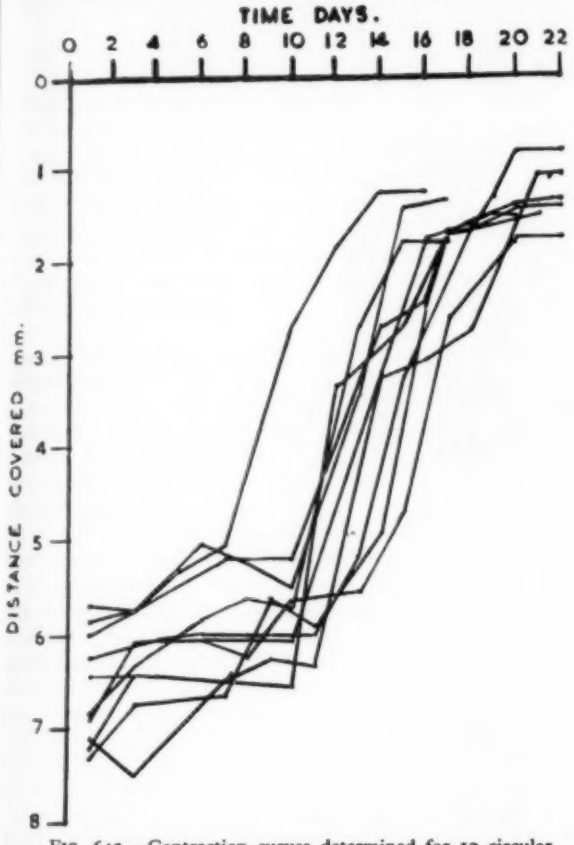


FIG. 645.—Contraction curves determined for 10 circular flank wounds in rabbits, selected at random, plotted as average decrease in radius with time, that is, the linear growth rate. The mensuration relates to the approximation of the *old* epithelial edge; the residual deficit at the termination of contraction (mean approximately 1·4 mm. in radius for this set of wounds) represents the size of the *new* epithelial regenerate.

difference in rate of growth, which exists in this comparison, would in fact be accentuated under conditions of comparable vascularity, which has been shown to influence greatly the rate of growth of granulation tissue.

Owing to the difficulty in determining an exact end point for contraction, the shape of the actual growth curve cannot be relied on in its terminal portion. However the growth curves clearly indicate that the absolute linear rate of contraction is constant for at least the major portion of the growth curve, an observation confirming the results of Henshaw and Meyer (1943). The findings of Burrows (1924) that the speed of contraction progressively increases, and of Carrel and Du Nouy (Du Nouy, 1936) claiming an opposite result, is not confirmed, although in the case of these investigations the use of area as a means of mensuration makes the results difficult to interpret. Observation of the healing wound clearly indicates that rapid contraction ceases as soon as epithelium covers the wound. From then on, not only does remodelling with retraction occur in the 'old' skin but the actual *new* regenerate (epithelium and

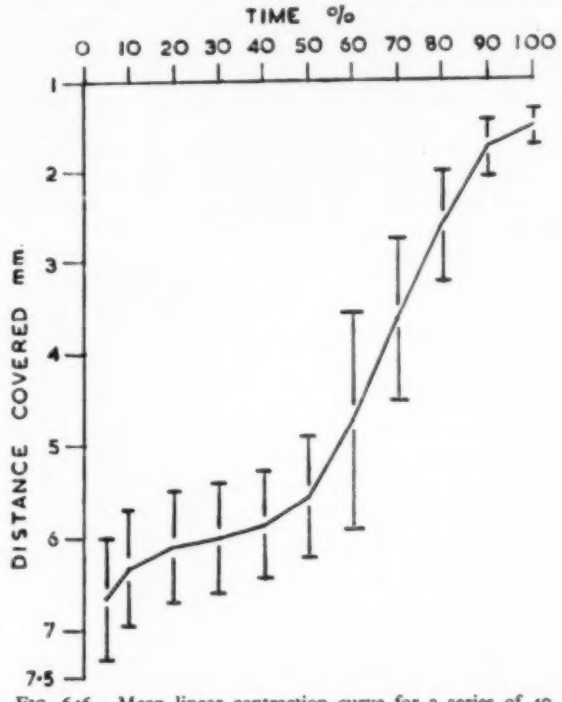


FIG. 646.—Mean linear contraction curve for a series of 40 flank wounds in the rabbit.

granulation tissue) at the centre shrinks, as observed by Carrel and Hartmann (1916), this process taking a relatively long time in comparison with the phase of contraction. It is suggested that this latter phase is the true expression of collagen dehydration and shortening and can be more appropriately designated *cicatrization*, as opposed to the contraction phase, which occurs earlier, more rapidly and is not accompanied by scar tissue formation. The old epithelium in contraction does not exhibit the altered texture of regenerated epithelium, which never qualitatively measures up to the adult host tissues, a feature of regeneration following injury which has been elucidated by Burrows (1932).

4. Onset of Epithelial Regeneration.—It is certain, from both histological studies and careful examination of wounds in the living animal, that epithelial regeneration occurs early, whether or not contraction occurs in a wound. This is a much slower process for reduction in size of a wound than contraction. However, the impression has been that epithelialization is more rapid in wounds which do not contract. The curve for wound healing illustrated by Du Nouy (1936) gives a fallacious impression of the part played by epithelialization in a contracting wound, and suggests that epithelial regeneration commences as an epimorphic phenomenon when contraction ceases. This is not confirmed by the present studies, or by the careful

observations on epithelial migration and regeneration in small wounds in fishes and amphibia by Arey (1921, 1932 a), and later in mammalian corneal lesions (Arey and Covode, 1943). Earlier, Loeb (1898) also described epithelial migration in experimental wounds in the guinea-pig ear, but his account of the histological changes, particularly in reference to scab formation, is open to criticism (Florey, 1954). Loeb's contention that contraction is a late phenomenon, due to contraction of granulation tissue which has filled a defect, is completely negated by the observations which have been recorded here and earlier by the pioneer studies of Carrel and his co-workers, and obviously confuses contraction with cicatrization.

5. Effect of Wound Size on Contraction.—For a small series of 8 flank wounds in rabbits of average radius 8·5 (± 1·7) mm., the rate of contraction was 0·64 (± 0·23) mm. per day, and the size of the residual area comprised of new regenerated epithelium measured 1·75 (± 0·55) mm. in radius.

It appears that the absolute linear rate of contraction is constant for wounds of different size, provided that the wounds are not of a size which bring into consideration secondary complicating factors, such as altered tissue rigidity. These data confirm the conclusions reached by Henshaw and Meyer (1943), and a recalculation of the data of Young and others (1941), in terms of linear growth rate, gives similar results.

MODIFYING FACTORS IN CONTRACTION

It is difficult to determine from the literature the meaning of many results in which agents have been employed to modify wound healing, owing to contradictory results, and failure to incorporate an analytical approach to the different processes concerned in wound healing, in appraising the effect of various substances. Arey (1936) has attempted to indicate some of the results obtained. However, the conflicting views on the actual nature of contraction, and its confusion with late cicatrization, gives rise to very little information which can be interpreted in a definite way. A series of experiments has been performed as a preliminary attempt to elucidate the nature of this process, and will be presented in combination with such relevant data as have been obtained from the literature.

1. Effect of 'Coverage' on Wound Healing.—Carrel (1921) showed that if a wound is covered with a thin layer of cellophane so as to seal the surfaces contraction is largely inhibited. The same applies to covering the wound with a skin graft. These observations are amply substantiated by clinical experience of wounds healing under protective dressings and plaster; epithelial regeneration occurs but contraction is largely inhibited. In experiments to be discussed later, it has been found that in the rabbit ear, if a wound is covered by perspex, virtually no contraction occurs and the entire deficit is reconstituted by the epimorphic regeneration of new tissue (*see below*). It is to be noted that in modern surgical practice the process of contraction has been largely eliminated, not only by surgical apposition of wounds, but also by the almost universal use of protective dressings on granulating surfaces and the extensive use of plastic procedures. However, in certain situations, the phenomenon of contraction is all-important in the healing of wounds with tissue loss. This applies particularly in the healing of deep deficits, for example perineal wounds following abdominoperineal resection of the rectum, drainage of an ischiorectal abscess, and excision of a fistula-in-ano; here the rapidity with which the wound heals is almost entirely due to contraction—not only of skin but of all the tissues lining the deficit. Thus the altered topography of the bladder base and pouch of Douglas following perineal resections in an expression of contraction. The conception, commonly expressed in surgical pathology texts, that the healing of large deficits is due to the 'filling in' with new granulation tissue and epithelial regeneration is entirely fallacious.

The interpretation of the effects of coverage on the contraction process is difficult. Most types of coverage tend to impose mechanical stresses, but Carrel's experiments with cellophane and free skin grafts suggest that the effect is not simply due to induced mechanical stresses. Carrel took the view that the protective surface prevented granulation tissue development, and that contraction depended quantitatively on the formation of granulation tissue. This view is subject to the criticism that thermal wounds freely granulate and epithelialize but fail to contract.

The importance of induced mechanical stresses and existing tissue tensions on the contraction process is clear. Wounds of the integument in sites where tissues are fixed largely fail to contract, but a plastic procedure which removes the cause of the tension and fixation allows for normal contraction. In deep wounds, e.g., perineal cavities, the most mobile tissues (skin and soft tissues of the peritoneal sacs) contract most readily; this observation is the basis for the time honoured surgical principle in anal surgery involving liberal excision of skin and the use of light packing to allow uniform synchronous contraction, and to prevent 'pocketing' and abscess formation. This is also the basis for the use of marsupialization in surgical practice.

2. Thermal Injuries.—It is a well known observation that thermal injuries, despite the profuse formation of granulation tissue and epithelial regeneration, largely fail to contract. This results in the poor general cosmetic results of thermal burns, which is due not only to thickening and cicatrization, often with keloid formation, but also because the size of the original deficit is not reduced appreciably by contraction, almost the entire process of regeneration being one of epimorphosis. If indeed, contraction is due to the formation of collagen and its subsequent shortening, one would expect this process to take place freely in the healing of thermal burns, which is characterized by the free formation of connective tissue fibres. On the other hand it is conceivable that the œdema which accompanies thermal burns leads to increased fibroplasia, which prevents the expression of contraction.

3. Infection.—If a wound becomes infected, with swelling and congestion of the margins, contraction is inhibited till the infection subsides. Contraction may recommence, although often at a much reduced rate with early cessation; restoration depending to a larger extent on epimorphic processes. However, observations on rabbit ear chambers show

that infection is compatible with the growth of granulation tissue unless the tissue is bathed in free pus, which causes a destruction of growing buds and newly formed tissues ; indeed low grades of infection lead to pronounced capillary regeneration and fibroblast migration. When infection subsides in an ear chamber, the formed regenerate shows development of fibroblasts and fibre in excess of normal. Again, a single dose of the order 2000 γr is necessary to inhibit the migration of epithelium.

These results indicate that profound differences exist between the essential nature of wound contraction on the one hand, and epimorphic regeneration in wounds on the other. The effects of ionizing radiations on developmental and regenerative processes in lower animals has resulted in similar findings

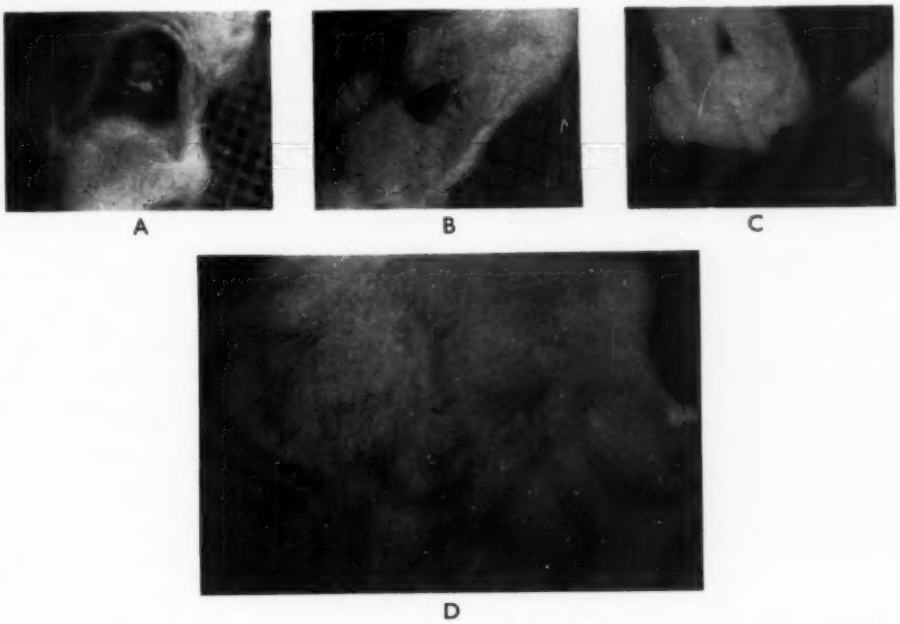


FIG. 647.—Healing of exposed wound in a rat (No. 24), initial size approximately 4·5 cm. in diameter. The full thickness of skin and subcutaneous tissues down to the dorsal musculature has been excised. A, 3 days after operation, B, 15 days, C, 24 days, D, rats 23 and 24, with identical initial sized wounds killed at 44 days. Note small irregular area of epithelial regeneration surrounded by clipped hair of original epithelium in C.

this observation is difficult to reconcile with the view that contraction is due to the development and shortening of collagen.

4. Ionizing Radiations.—Ionizing radiations have been used as a formal technique in morphological analysis and experimental embryology. The application of this method to a study of the processes involved in wound healing has been employed by the writer, and is reported elsewhere in detail. A determination of the survival curves for different aspects of regeneration in wound healing, with increasing doses of irradiation of the same quality, has shown that the growth of granulation tissue behaves very differently from the contraction of a wound in the same animal, when subjected to ionizing radiations. For growing granulation tissue in rabbit ear chambers, a single dose of γ-rays from Co^{60}, of the order 2000 γr, is necessary to inhibit regeneration ; lower doses fail to alter the tempo of the regenerating process significantly, a very steep survival curve of the 'all or none' type being obtained (van den Brenk, 1955). In the case of a contracting wound in the rabbit, irradiated after operation, it has been determined that a significant decrease in the tempo of contraction is obtained with doses as low as 500 γr, the rate of contraction decreasing progressively with increasing doses of irradiation (to be published). Preliminary studies on the regeneration of epithelium in specially designed perspex chambers in the rabbit's ear indicate that (Curtis, 1936 ; Brunst and Scheremetjewa, 1933 a, b ; Horn, 1942), with variations in radio-sensitivity amongst the different components which constitute the regenerate, giving rise to both quantitative and qualitative deficiencies.

5. Contraction in Other Animals.—Contraction of wounds and injured tissues is widespread throughout the animal kingdom, and occurs in all tissues in which inherent rigidity of construction does not prevent the free movement of cells and remodelling processes. In rodents, extensive wounds of the integument result in rapid contraction and closure. A wound involving the full thickness of the integument in the middle of the back of a rat, 4 cm. in diameter, closes within 25 days almost entirely by contraction, the original wound site being almost invisible (*Fig.* 647). In the human, modern surgical practice largely intervenes in the normal expression of contraction in wounds of the integument and elsewhere. However, that it does occur was amply proven by the pioneer studies of Carrel in this field, and in *Fig.* 648 is shown a healed wound on the inner surface of the thigh, in which a circular deficit due to sloughing from an irritant hypodermic injection, over 6 in. in diameter, contracted to one of about 1 in. in diameter, the central portion healing by epithelial regeneration. It is of surgical importance that skin healing which occurs by contraction gives almost perfect cosmetic results and mobile tissues, with minimal deformity, and should not be confused

with the deformity due to late cicatrization, and the qualitative deficiencies associated with regenerated epithelium and granulation tissue.

THE NATURE OF CONTRACTION

A review of the literature clearly reveals that interpretations of the process of contraction in mammalian wounds have been largely based on

FIG. 648.—Healed wound on inner surface of human thigh. The wound which resulted from sloughing of skin and underlying tissues, originally measured approximately 10 cm. in diameter, and was treated by the patient with a plain gauze dressing, but largely left to form a scab, and heal exposed to the air. The residual size of the epithelial regenerate, 12 months after injury, was 3 cm. in diameter. The residual cicatrix is quite mobile on underlying tissues, the regenerated epithelium is thin and pigmented, but the 'contracted' epithelium is qualitatively normal, except for scattered foci of pigmentation.

equivocal quantitative data, inaccurate observation, and a pre-conceived notion that contraction implies a chemical shrinkage of some substance, which has been automatically identified with collagen fibre. A short account of some of the views held on the biological processes resulting in closure of wounds in mammals is not out of place. Eberth (1891) considered closure to be entirely due to cell proliferation, that is to say mitosis, occurring in all tissues of the integument; Werner (1902) considered increase in cell size also important, and looked on contraction as essentially due to shrinkage of the 'young cicatrix' (presumably granulation tissue). Born (1897) clearly recognized wound contraction and considered this process took place as a result of passive centripetal mechanical forces. Carrel (1910, 1912) is the first writer to give a clear account of contraction in mammalian wounds. He recognized that after a latent period of approximately one week in dogs and humans, a sudden progressive reduction in size of an exposed wound occurred which involved the *original surrounding tissues*, and was quite distinct from the epimorphic regeneration of epithelium and granulation tissue, although the fact that the latter occurred simultaneously suggested to Carrel that the growth and maturation of granulation tissue was the cause, *per se*, of contraction. This led to his use of the term 'granulous contraction'. Carrel considered contraction due to shrinkage of young granulation tissue. Burrows (1924) was more hesitant in accepting shrinkage of the tissues of the wound margin as solely responsible for contraction; he recognized that both epidermis and corium are involved, and that contraction continues to the limits of their elasticity until connective tissue overgrowth and epithelial regeneration fills the intervening gap and prevents further contraction. Burrows confirmed Loeb's earlier observation that mechanical rigidity and fixation of tissues prevents contraction, closure then being due to epithelial migration and regeneration, *pari passu* with granulation tissue formation. Burrows considered that contraction of epithelium was due to unknown intrinsic forces within the old marginal epithelium, probably associated with cell proliferation, the epithelium 'sliding' over the underlying corium. The importance of amœboid activity in healing tissues was first suggested by Klebs (1875). This observation has been confirmed and extended by the studies of Arey (1932, 1936; Arey and Covode, 1943) on the regeneration of epithelium in small wounds in fishes and amphibia, and mammalian corneal wounds; by Oppel (1912) in tissue culture; Holmes (1914) in adult and larval amphibian ectoderm; Poynter (1919) in ectodermal wound healing in the chick embryo; and many others (*see* Arey, 1936, and Cameron, 1952, for reviews). Views expressed more recently on the nature of contraction in mammalian wounds have not carried conviction and, strangely enough, often infer doubt that the process is a reality in the healing of mammalian wounds. Arey (1936) takes the view that "retraction and contraction of the wound probably represent, for the most part, secondary (and in a sense, accidental) features . . . however important they may become from the practical point of view", and again "retraction is a purely mechanical phenomenon, while contraction is surely due in considerable measure to the production and subsequent shortening of connective tissue fibrils". Needham (1952) states that wound "closure is facilitated by a prior contraction of the collagenous connective tissue fibres of the dermis, which are augmented by the activity of fibrocytes penetrating the clot in the wake of the phagocytes". Cameron's (1952) analysis of wound healing briefly refers to Carrel's classification of the sequence of events in wound healing, without comment, and emphasizes the morphological changes in connective tissues without clearly defining the stages at which contraction and subsequent cicatrization occurs, and any of the qualitative and quantitative differences in the connective tissues at these times. Florey (1954) states: "According to some observers, the early closing of open wounds, at any rate in the loose skin of animals, is greatly assisted by a contraction that affects both the corium and epithelium. This contraction, which is possibly due to a layer of muscle in the skin, may contribute more to the closing of the wound than actual epithelialization. Precisely how this initial contraction is brought about is not clear, but in the later stages the contraction of newly formed fibrous tissue no doubt plays a considerable part."

The salient facts which are available in relation to wound contraction, and which have been indicated already, may be summarized as follows:—

1. *Contraction* occurs early in the healing of wounds with tissue loss, in those tissues where mechanical rigidity does not prevent its expression. It gives rise to minimal deformity and scarring. This is in striking contrast to *cicatrization* which develops slowly and late in the healing process, usually after a wound is closed, and occurs despite considerable mechanical rigidity and often gives rise to striking deformities and scarring, both in the integument and in deep tissues subject to skeletal support (e.g., spinal curvature following chronic empyema).

2. Whilst contraction is accompanied by the formation of granulation tissue, which appears to act as an essential concomitant in the healing of wounds of the integument, at least partly acting as a protective membrane (Billroth, 1865; Melchior and Rosenthal, 1920) against infection, and partly contributing to the digestion of fibrin and other components of the clot (Burrows, 1924), the amount of granulation tissue formed bears no direct relation to the ease with which contraction takes place in wounds. In general the opposite holds. In the healing of thermal burns, and infected wounds, the abundant formation of granulation tissue is not accompanied by a proportional degree of contraction—in fact the latter largely fails to take place. However, in this type of wound, late cicatrization is predominant and is clearly related to the size of the newly formed repair blastema. Why contraction is largely inhibited in burns is not clear. It would appear that before contraction can take place the demolition phase in wound healing (Needham, 1952) must be completed. In thermal burns, a zone of necrobiosis as postulated by Borst (1920) in his ' third zone of tissue injury ' may occur, with cells either undergoing slow death or recovery, giving rise to a prolongation of the demolition period, and protracted traumatic inflammation, which is incompatible with contraction, perhaps for mechanical reasons, but allows for epithelial regeneration and migration over the formed granulations.

3. There is a distinct difference between the latent periods for the growth of the repair blastema and contraction; this difference also applies to the absolute linear rates of growth in the two processes (*see above*). The conception that tissue deficits due to trauma undergo spatial restitution by the epimorphic regeneration of epithelium and the repair blastema in mobile tissues is not in accordance with common observation in experimental pathology and clinical practice. It is emphasized that, in surgical practice, contraction is responsible for quantitative reductions of over 90 per cent in certain sites and conditions.

4. Contraction occurs in all types of mobile tissue, and is apparently widespread in the animal kingdom. Its occurrence in skin cannot be attributed to the presence of a muscular layer, it occurs whether this layer is absent, excised in continuity, or left behind. Contraction also involves any cellular tissue, and does not depend on the presence of skin, with a " moving forward of the epithelial layer and a dragging of the whole skin with it ", as envisaged by Burrows (1924). However, the rates of contraction in different tissues vary considerably, largely due to different mobilities; this has an important application in surgical practice, and the adoption of marsupialization and related techniques in wound management, already discussed.

5. Ionizing radiations cause a depression of both the onset and rate of contraction, and also reduce the rate of growth of both granulation tissue and epithelium. However, the survival curve obtained for contraction differs profoundly from that for the repair blastema (granulation tissue). Doses of irradiation, which cause vascular destruction in the growing repair blastema, without causing cessation of fibroblast migration, would be expected to enhance contraction in accordance with the collagen formation hypothesis. Actually, such doses cause not only prolongation of the latent period for contraction but also a reduction in the rate of contraction (*see above*). A detailed account of these findings is to be published later. However, it would appear that the explanation for the prolongation of demolition period is due to the added destruction of the more radio-sensitive elements in the tissues, similar to that in thermal burns, the more ' proportional ' effects with ionizing radiations being due to the accuracy with which graded doses of this type of injury can be administered, uniformly, and the effects determined. If one half of a wound is shielded during irradiation, normal contraction of the unshielded sector occurs, the irradiated sector behaving in accordance with the dose administered.

6. The non-irritant coverage of a wound, by cellophane, perspex, or autogenous skin graft, inhibits contraction, but allows epimorphic regeneration to take place (*see below*). These findings, first determined by Carrel, are probably not due for the most part to the creation of mechanical rigidity which inhibits contraction. Carrel and Du Nouy (Du Nouy, 1936) interpret these observations in the light of the amount of granulation tissue formed. They consider that irritants promote granulation tissue formation and, therefore, contraction. However, this observation needs to be confirmed; it is doubtful if an irritant promotes contraction as opposed to cicatrization. In the case of a rigid scab which provides cover, progressive digestion and loosening with establishment of a zone of discontinuity is the rule and cannot be logically compared with protective indigestible or living covers. Although the explanation of the effects of coverage on wound contraction is not clear, it appears that an equalization and stabilization of abnormal differential tissue tensions created by injury and the progressive loosening and digestion of a scab are important factors.

7. Cortisone in large doses tends to cause abnormal changes in the growth of the repair blastema in Sandison Clark ear chambers (Ashton and Cook, 1952) but still allows for progressive growth to occur, as determined by the writer (unpublished). It has been found that cortisone in moderate dosage decreases the rate of contraction, and prolongs the latent period. The interpretation of these findings is doubtful; that connective tissue growth and development is reduced by cortisone has been shown, but further studies are necessary to determine the effect of cortisone on the rate of cellular migration in general and to elucidate the part played by constitutional factors in wound healing in cortisonized animals.

RELATIONSHIP OF CONTRACTION TO MORPHYLLAXIS

The replacement of lost parts by remodelling of the remainder characterizes morphyllaxis (Needham, 1952). It occurs essentially in mobile tissues where tissue rigidity, incurred by the presence of skeletal systems, does not prevent its manifestation. Morphyllaxis is, therefore, most prominent in the lower invertebrates, in contrast to the Arthropoda and higher forms, where remodelling is restricted to local de-differentiation prior to formation of the blastema, adjacent to the wound surface. In many organisms, a close integration of morphyllaxis and epimorphic regeneration occurs in the restitution of body form following injury; in annelids cephalic segment replacement proceeds not only by epimorphosis, but also by a remodelling of the appropriate number of anterior segments of the parent piece (Korschelt, 1927). Morphyllaxis begins near the blastema (or surface of amputation), and progresses proximalwards (Abeloos, 1930, 1932), a continuous gradient in morphogenetic activity existing from the blastema through all grades of morphyllaxis to completely unmodified tissues. It is stressed that epimorphosis and morphyllaxis are not strictly independent and distinct processes in normal regeneration and healing; there is an essential unity in the whole process (Abeloos, 1930; Child, 1941; Davidson and Berrill, 1948; Needham, 1952); morphyllaxis acting in a complementary way to epimorphosis if organization is sufficiently plastic to permit remodelling at all. In mammals, the latter condition holds in certain situations and morphyllaxis occurs, as in compensatory and functional hypertrophy, and in the maintenance of adult form, even where total size does not increase.

It is obvious that a remodelling process like morphyllaxis is more concerned with migration of cells than cell division (mitosis). Child (1941) has supported this view by the finding that morphyllaxis is not sensitive to nutritional variations, as opposed to epimorphosis. It is suggested that contraction in mammalian wounds behaves essentially as a morphyllactic phenomenon, and much of the evidence discussed above fits in with this conception, which would bring this feature of wound healing into line with the classification of healing processes accepted in comparative morphology. The importance of contraction, in restitution of mammalian wounds, makes one diffident in taking Arey's (1936) view that it is of the nature of a biological accident. The close integration of morphyllaxis and epimorphosis, already pointed out, would go far in explaining the close interdependence of contraction and establishment of the repair blastema, and divert attention from collagen shortening as the cause of contraction, to a morphological phenomenon common to regeneration in animal life. Needless to say, morphyllaxis, and indeed all growth, is unexplained in formal physicochemical terms. However, it appears from certain studies (Coe, 1929; Abeloos, 1930; Child, 1941) that there is probably a common organizer for both epimorphic and morphyllactic components in regeneration; in planarians and nemertines this organizer has been found to reside in the blastema itself.

EPITHELIAL REGENERATION

The observation and measurement of epithelial regeneration as an epimorphic process in wounds, free from errors of interpretation introduced by the occurrence of contraction, presents many difficulties. The continual removal of the scab in healing wounds in an attempt to measure ' healing under a scab ' gives rise to circumstances incompatible with reliable values for either contraction or epithelial regeneration, and introduces a serious experimental factor namely, continuous trauma and tissue destruction, which has to be evaluated in any quantitative and qualitative studies.

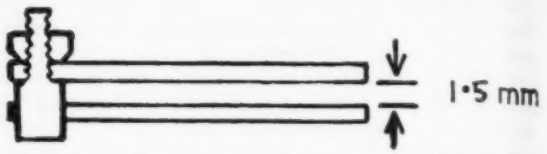


FIG. 649.—Cross sectional diagram of ear chamber used for observation of epithelial regeneration. The dimensions are identical to those for Sandison Clark type ear chamber in *Fig.* 628, except the lower plate has no central table, and the distance between the two plates is fixed according to the thickness of the ear (approximately 1·5 mm.). Only one of the three pillars is shown.

A simple method has been devised which permits accurate measurement and observation of epithelialization in a sterile covered wound in a rabbit's ear, free from contraction. The observation. of Carrel and Du Nouy (Du Nouy, 1936) that a wound covered by a non-irritant substance fails to contract has resulted in this technique which will be described together with some of the results obtained.

EXPERIMENTAL METHODS

Rabbits with moderately long ears are used. The ears are closely clipped, but not shaven. The animal is anæsthetized, the ears thoroughly washed with detergent and soaked in antiseptic (acriflavine). Under full aseptic precautions the ear is transferred to a wooden shaped block, and held moderately stretched with the outer surface uppermost. A circular impression of the desired size (0·5 cm. to 1·5 cm. in diameter) is made on the skin with a punch. The full thickness of epithelium inside the circle is then removed from the underlying dermis and blood-vessels, care being taken to cut the skin perpendicularly and not to leave behind any hair follicles which may give rise to foci of regeneration. Hæmostasis is effected by the use of pressure if bleeding occurs, no suture material is used, and a cautery avoided.

A perspex template with three outer holes corresponding in position to the pillars of the chamber is held on the ear, and centred on the wound. Three holes are punched through the entire thickness of the ear. The lower portion of the perspex chamber with pillars attached is then introduced from the inner surface of the ear. The *inner* surface of the perspex ' cover-glass ', that is, the surface to be apposed to the wound, is first given a coating with ' Vaseline ', to form a thin annulus at the extreme periphery of the cover slip. As an alternative procedure, the holes are punched before the skin is dissected.

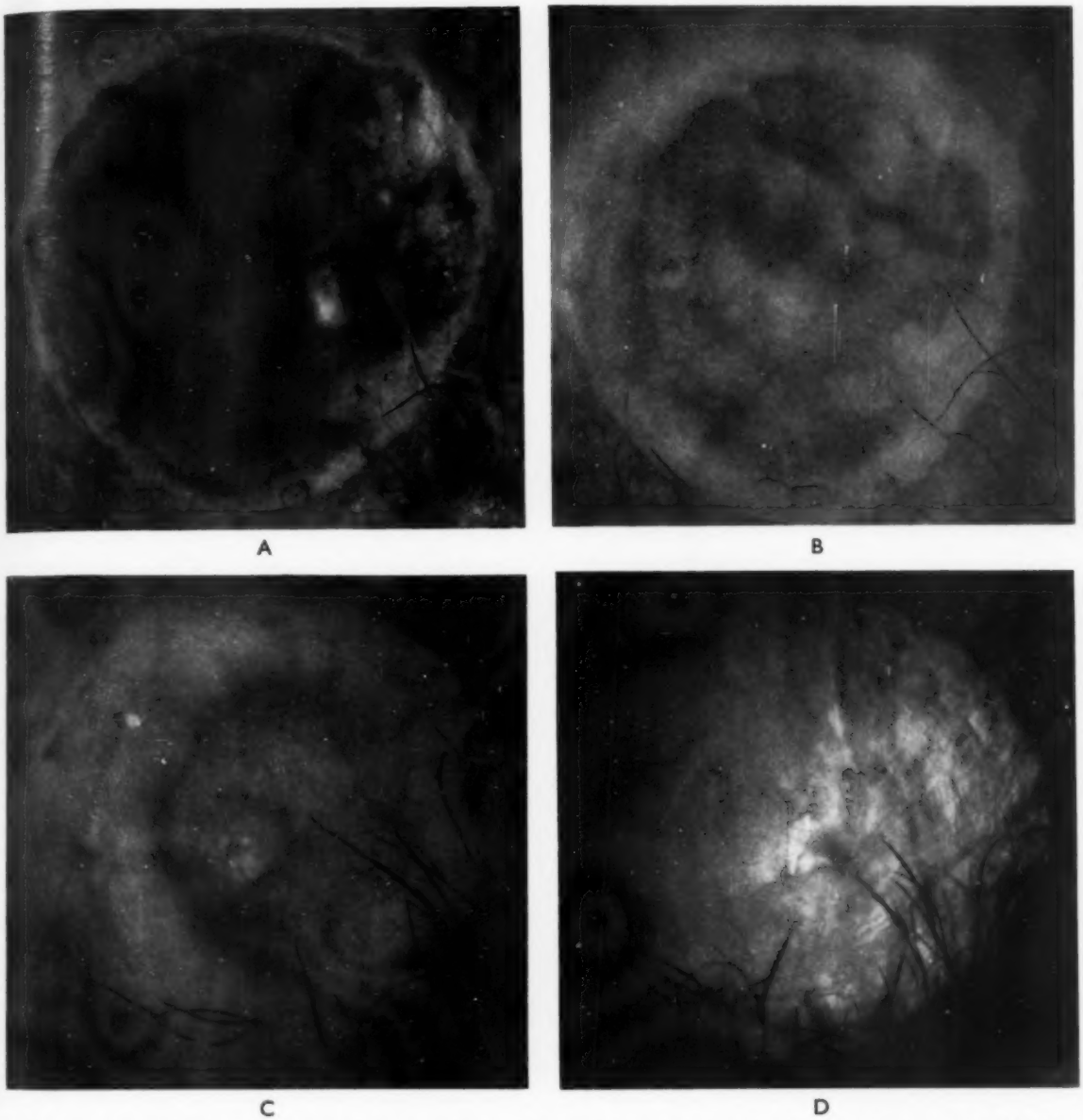


FIG. 650.—A circular wound in the rabbit's ear healing under a sealed perspex cover (*see Fig.* 649), by means of epithelial regeneration, without significant contraction. A, 10 days after operation; B, 17 days; C, 27 days; D, 58 days. (× 6.)

DESIGN OF CHAMBER

The dimensions closely follow that described above for the modified Sandison Clark ear chamber. The lower plate, however, is a plain perspex disk, without a raised platform. The pillars and coverslip are assembled in the same way but the distance between the cover and base is determined by the thickness of the ear measured with callipers (averages 1·0–1·5 mm.). A gauge of the correct thickness is introduced between cover and base, with the pillars firmly bolted to the cover, and the pillars are then fixed to the base with solvent (*Fig.* 649).

PHOTOGRAPHY

The whole wound area is photographed every second day (daily if necessary) with indirect (reflected) light, using a 3 to 1½ in. photomacrographic lens.

EXPERIMENTS

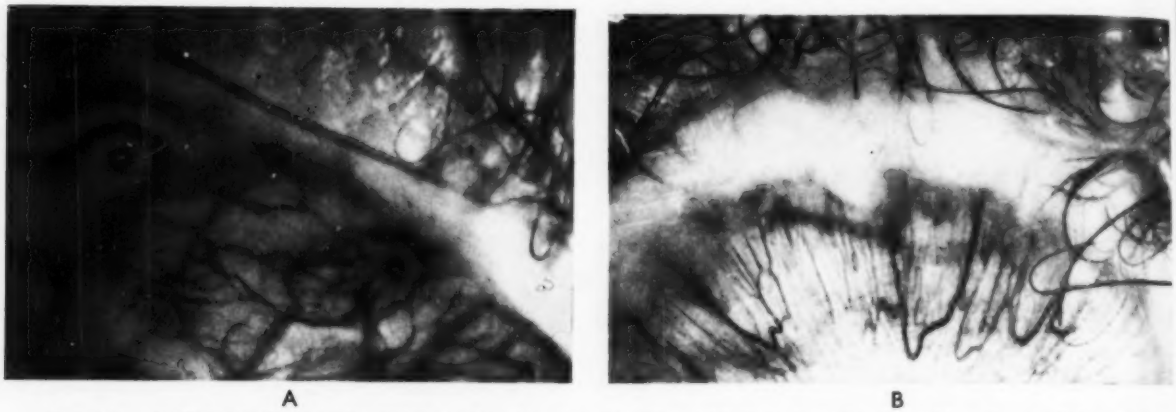
In accordance with the above technique, the behaviour of wounds of diameters ranging from 6·0 mm. to 25 mm., have been observed, measured and the growth curves for the absolute linear rate of growth determined by the methods of enlargement and mensuration adopted for contraction (*see above*).

RESULTS

1. Qualitative.—For a few days a thin layer of blood-clot and exudate covers the wound. During this time a progressive absorption of the clot occurs, and this demolition period is usually completed in approximately five days. At the end of this time, the old epithelial edge is clearly visualized and an orderly new formation of capillary loops have

appeared which are orientated with their convex surfaces directed towards the epithelial margin. From this time onwards a progressive regeneration of epithelium in continuity with the old epidermis takes place. This regenerated epithelium appears as a pale, translucent growth, growing in centripetally from the wound margin, and is clearly distinguishable from the old epidermis, with its hair follicles and

c. The average rate of regeneration of epithelium, namely 0·207 mm. per day for wounds averaging 5·17 mm. in radius, is approximately one third that for the rate of contraction in flank wounds of a similar size (0·65 mm. per day for wounds averaging 6·63 mm. in radius), whilst the average linear rate of growth obtained for the repair blastema in ear chambers is 0·094 mm. per day.



A B

FIG. 651.—A, Showing the vascular pattern at the edge of regenerating epithelium, in a chamber. Note the parallel arrangement of vessels in the granulation tissue, forming loops at the migrating epithelial margin. B, Showing the vascular pattern at the edge of regenerated epithelium, six months after growth had ceased in a large wound (2·5 cm. diameter circle). Note the appearance of mature large vessels and the absence of the typical loop formation at the epithelial margin. (× 12·5.)

opaque appearance (*Fig.* 650). As the epithelial growth spreads inwards a progressive alteration in vascular pattern occurs, so that there is always a marginal formation of capillary loops in juxtaposition to the growing edge, the stems of the loops being orientated radially at right angles to the growing edge. (*Fig.* 651.) With ageing the regenerated epithelium becomes less translucent and thicker, and also has a striated appearance in the form of regular concentric rings. If the cover-slip is removed from the chamber and the wound examined before regeneration is completed, the regenerated annulus has a dry but translucent appearance, whilst the portion of the wound not covered bleeds after the manner of ordinary granulation tissue. In the regenerated epithelium, regeneration of hair follicles and growth of hair has never been observed to take place.

2. Quantitative.—With wounds less than 1·5 cm. in diameter, a progressive orderly regeneration of epithelium to completion occurs in the absence of infection. Two growth curves for wounds averaging 3·19 (± 0·08) mm. and 5·17 (± 0·18) mm. in radius respectively, each curve representing the mean for six wounds, are in *Fig.* 652. The absolute mean linear rates of growth for the two sizes of wound were 0·208 (± 0·017) mm. per day and 0·207 (± 0·048) mm. per day respectively. In both cases the growth curve for the absolute linear growth rate is essentially a linear relationship for the major portion of the regeneration process. It is to be noted that :—

a. As for contraction and growth of the repair blastema, the absolute linear rate of growth for the epimorphic regeneration of epithelium gives a similar type of growth curve that is essentially linear throughout.

b. The latent period for epithelial regeneration is considerably less than half that obtained for contraction in flank wounds.

d. The mean rate of growth for epithelial regeneration in wounds of less than 1·5 cm. in diameter is independent of wound size.

With wounds of size greater than 1·5 cm. in diameter, epithelial regeneration commences in a similar way, but after the epithelium has grown in for a distance of approximately 7·0 mm., growth often ceases abruptly, and further regeneration fails to take place, despite what appears to be satisfactory conditions, viz., absence of infection and completion of the demolition phase. This cessation of growth is always associated with a disappearance of capillary loops at the growing edge, and an apparent maturation of the central vascular bed, with the appearance of large blood-vessels. Wounds have remained quiescent in this condition for periods of six to nine months, without infection but some tissue distortion and considerable 'drifting' of the chamber takes place, apparently associated with late cicatrization (*Fig.* 651 B).

DISCUSSION

The regeneration of epithelium, as an epimorphic process in wound healing, occurs in direct continuity with existing epithelium, and in accordance with Flexner's Law, that tissues retain their specificity, it is generally conceded that epithelium only arises from epithelium. However, the occurrence of radical metaplasias in vertebrates have been described. Rose (1948) considers that epidermal cells may give rise to the mechanocyte tissues of the blastema in amphibia. A similar view, based on grafting experiments in the axolotl, is held by Umanski (1938), whilst Levander (1945) expresses the opinion that dermal tissues may give rise to epidermis in the mammal. Whilst the reality of such transformations cannot be entirely discounted, much of the evidence on which reliance is placed is of a dubious nature.

It is apparent that the appearance of cells, during the stage of de-differentiation of the blastema which accompanies and follows the demolition period, gives rise to much confusion in the morphological evaluation of tissue types by the formal techniques of morbid histology. The observation of behaviour of tissues *in vitro* (Willmer, 1947) has led to the conclusion that metaplasia does not occur between epitheliocyte and mechanocyte tissues, *in vitro*, and observations of epithelial regeneration in rabbit ear chambers (Clark and Clark, 1944) give rise to similar conclusions, *in vivo*.

That migration plays a primary role in the regeneration of epithelium has been recognized for a long time (*see* Cameron, 1952, for review of earlier literature). The earliest description of migration, based on histological studies is that of Loeb (1898). For large wounds in the pigeon, rat, and guinea pig, a marked increase in mitotic rate proportional to the size of the defect occurs in the old epithelium, especially near the surface of amputation, as long as the wound is open. The mitotic rate is at first reduced in the out-growing epithelium, with a sharp rise after a few days, and with maximal activity at the time of closure (Spain and Loeb, 1916; Loeb, 1920). Also, an increase in cell size of 39 per cent has been described in the old adjoining epithelium and in the new growing layer (Spain and Loeb, 1916; Akaiwa, 1919). The role of migration is even more clearly demonstrated in later studies on small wounds. Various workers have shown that mitotic activity is inappreciable in the healing of small wounds (Arey, 1936; Wigglesworth, 1937; Wilbur and Chambers, 1942). In fishes and amphibia, mitotic activity is a completely inadequate explanation for the healing of small wounds (Arey, 1932 a); even large wounds in fishes heal, in the absence of mitosis in either epidermis or connective tissue (Harabath, 1928). For small corneal wounds in mammals, wound healing took 6–10 hours, with an actual decline in mitotic activity during restitution, and for the first days following injury, to less than half normal; a normal rate was established on the fourth day after healing, and on the fifth day the mitotic rate exceeded normal by 75 per cent (Arey and Covode, 1943). For wounds in *Necturus*, similar changes take place, and the mitotic activity increases to 135 times normal during the week following completion of wound healing (Arey, 1932 a, b).

The implication of these results, on the interpretation of a growth curve obtained for epithelial regeneration (*Fig.* 652), is obvious. A curve, which is based on increase in cell number or size, is a legitimate expression of events, after healing is largely completed for this type of regenerate, and cannot be related to measurements of the size of the defect during restitution. The latter process, which largely results from cellular migration, as a directional phenomenon, is more truly represented by a curve which expresses the absolute linear rate of growth (migration).

The term migration, as applied to epithelial tissues, cannot be accepted as synonymous with amœboid movement (Florey, 1954). However, the use of the terms ' sliding ', ' moving ', ' stretching ', etc., in connexion with epithelial tissues is no less unacceptable. The term migration may be simply defined as the active spatial redistribution of a cell in the organism with time. This definition includes all types of locomotion, and also embodies certain active adjustments in the form of cell aggregates, in response to physicochemical and mechanical changes. Clearly the redistribution of epithelium which occurs

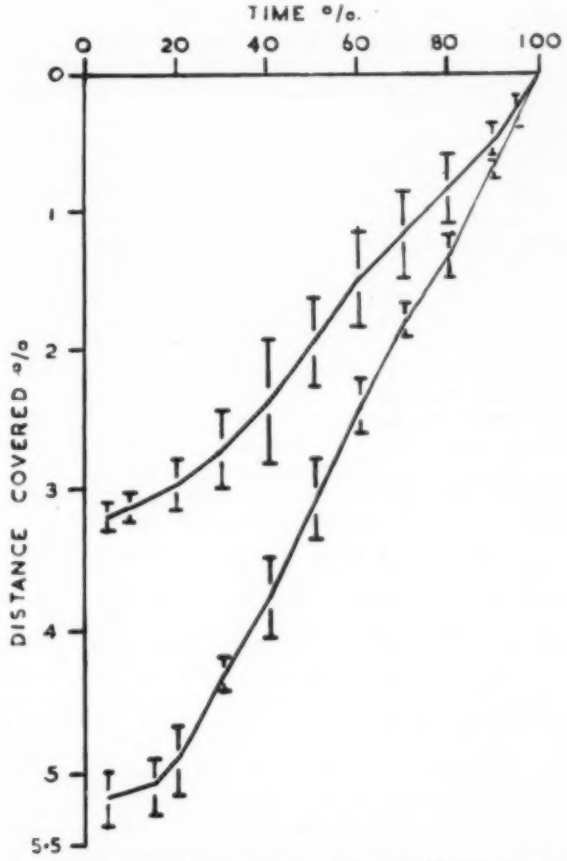


FIG. 652.—Mean growth curves for epithelial regeneration under perspex cover in the rabbit's ear for wounds of two different sizes.

in healing—both in morphyllaxis and epimorphosis—presents outstanding characteristics. Amœboidism, as defined by pseudopod formation and cytoplasmic streaming, is clearly much modified; although certain studies indicate that alterations in cell form of a definite pattern constantly accompany migration of epithelial cells (Clark and Clark, 1944).

Perhaps the most outstanding characteristic of epithelial migration is the phenomenon of thigmotaxis, that is, the covering of flat surfaces by cells maintaining intercellular contact during migration in the form of a flat sheet. The behaviour of epitheliocyte tissues in regeneration studies in the blood-sucking bug, *Rhodnius prolixus*, and the bed-bug, *Cimex*, by Wigglesworth (1947), suggests that there may be a chemical linkage between epidermal cells, enabling a multicellular aggregate to act as a ' chemical continuum ', in an integrated manner. This conception was earlier expressed by Heidenhain (1923) and later Fischer (1925) propounded the theory that unification amongst cells in a multicellular aggregate is secured by interchange of substances (' desmones ') by way of intercellular cytoplasmic bridges. The histological

demonstration of the latter in epithelial tissues is significant. Clearly this conception of unity of action in a cellular aggregate appeals in considerations on the nature of integrated regenerative processes (epimorphosis and morphyllaxis), and should be correlated with the dynamic changes in form which take place during de-differentiation, growth, differentiation, and remodelling processes—much of which is incomprehensible in terms of the behaviour of single cells. If the observation of Young and others (1941) that secondary wounds heal faster than primary wounds is correct in terms of linear growth rate, an explanation for the accessory accelerating factor which must operate may be more profitably sought in terms of an 'organ response to injury' than in 'constitutional' or 'general' causes associated with metabolic changes of inconsequential magnitudes.

The notion that epithelial migration, under a scab or under sterile cover, is a simple morphological event which can be studied as a phenomenon, isolated from synchronous changes which take place in the dermis, is clearly unwarranted. Epithelial migration does not occur until local demolition is complete, and is accompanied, *pari passu*, by continual ordered remodelling of the vascular bed or granulation tissue (*Fig.* 651 A), that is, regeneration is a 'mosaic progression', in which organizing properties can be attributed to the epithelium, however limited, and possibly showing progressive decrease during regeneration (Needham, 1952). The spontaneous cessation of epithelial migration which occurs in larger wounds, *see above*, (*Fig.* 651 B) may be attributed to a loss of organizer properties. However, the progressive fibrosis of the repair blastema with ageing may be an alternative explanation, and has clinical parallels in the cessation of regeneration in certain chronic ulcers (for example varicose ulcers). The experiments of Thornton (1949) with beryllium salts, which cause fibrosis and an accompanying loss of regeneration with the formation of a 'dermal seal', point to similar conclusions and have been interpreted as an induced inhibition of de-differentiation processes in connective tissues; this loss of powers of de-differentiation in a tissue may account for the limitations to regeneration encountered in both ontogeny and phylogeny (Goodwin, 1946).

CONCLUSIONS AND SUMMARY

1. The documentation of growth data for restorative processes in the healing of wounds with tissue loss has been based largely on measurements of size, i.e., cell number. This places the emphasis *during* regenerative processes on cell division (mitosis) and an implied chemical synthesis. However, the majority of investigations, dealing with mitotic counts in regenerates of various types, fail to substantiate that mitotic activity and cell reproduction is the active factor *during* regenerative processes—in fact, mitotic activity is often reduced below normal, and only becomes raised after restitution is complete, or at least, largely under way. It follows that a growth curve, which seeks to portray synthesis of living tissue in terms of size of a regenerate with time, documents an event which largely fails to occur over the period of observation.

2. For reasons which have been discussed a mensuration of regenerative processes in wound healing has been adopted, which is based on the principle that 'the *tactics* of regeneration, as of embryonic development, is primarily and fundamentally a matter of movement of cell substance, cells, and cell groups' (Medawar, 1947). It is suggested that the *absolute* linear rate of growth, of a regenerate, with time, is the relationship which can be justly and most profitably adopted in the documentation of data on wound healing and allied processes, a conclusion similar to that reached by Henshaw and Meyer (1943).

3. Growth curves have been established for three clearly identifiable regenerative processes in wound healing—namely the growth of the repair blastema, contraction, and the epimorphic regeneration of epithelium—by the measurement of these processes as separate entities in the rabbit. For this purpose, the Sandison Clark ear chamber has been utilized to measure the growth of the repair blastema. Contraction has been measured in undisturbed flank wounds in the rabbit, and a method of studying and measuring the epimorphic growth of epithelium in rabbits' ears has been described.

4. Whilst the rate of growth obtained for the three processes varies, each process also exhibiting considerable variation in individual growth rates, the *form* of the growth curve in each case is *essentially linear* throughout. This finding is considered to be consistent with the view already expressed, that the tactics of regeneration is essentially a matter of cell migration.

5. A mass linear curve of growth for restoration following injury, which is a composite record of several types of migration taking place, asynchronous in time and varying in rate, will clearly show departure from a linear form, even if the individual processes taking place exhibit a linear rate of growth throughout. This consideration warrants the analytical approach to wound healing which has been adopted, and the examination of separable entities. However, it is emphasized that a large bulk of the data, based on wound healing, essentially measures the dominant process, namely contraction. The desirability of distinguishing between the various regenerative processes in wound healing is also clearly indicated in bio-assay studies.

6. Further evidence as to the importance of migration in regenerative processes is presented in connexion with the regeneration of tissues of the repair blastema, observed in Sandison Clark ear chambers, particularly vascular regeneration.

7. The reality and importance of *contraction* in the healing of wounds are discussed. Evidence is presented that contraction cannot be categorically identified with the differentiation and shortening of collagen in granulation tissue, and a clear distinction is shown to exist between contraction and late cicatrization in wound healing. It is suggested that contraction is essentially a process of morphyllaxis, involving cellular migration and remodelling of tissues, and involves both epitheliocyte and mechanocyte tissues similar to morphyllactic phenomena which take place following injury in other tissues and organisms. The close integration of morphyllaxis and blastema formation and growth is closely paralleled by that of contraction and epimorphic processes in wound healing.

I wish to thank Professor David Slome and Professor Geoffrey Hadfield for their interest and encouragement; Dr. C. Cook, Institute of Ophthalmology, London, for his help in ear chamber techniques; Dr. H. A. Sissons, Institute of Orthopædics, London, and Dr. B. D. Wyke, Royal College of Surgeons, London, for much helpful advice and criticism. I am greatly indebted to Mr. R. D. Chambers for his highly skilled technical assistance, to Mr. S. P. Steward for making the ear chambers and the drawings in *Figs.* 628 and 631, and to Miss G. E. Angus for carrying out the measurements and calculations. I am grateful to Smith and Nephew Research Ltd. for a grant for equipment and the expenses of this investigation.

REFERENCES

ABELOOS, M. (1930), *Bull. biol.*, **64**, 1.
— — (1932), *La Régénération et les Problèmes de Morphogenès*, Paris.
AKAIWA, H. (1919), *J. med. Res.*, **40**, 311, 371.
ALGIRE, G. H. (1943), *J. nat. Cancer Inst.*, **4**, 1.
AREY, L. B. (1921), *J. exp. Zool.*, **33**, 463.
— — (1932 a), *Anat. Rec.*, **51**, 299.
— — (1932 b), *J. Morph.*, **53**, 367.
— — (1936), *Physiol. Rev.*, **16**, 327.
— — and COVODE, W. M. (1943), *Anat. Rec.*, **86**, 75.
ASHTON, N., and COOK, C. (1952), *Brit. J. exp. Path.*, **33**, 445.
BACKMANN, G. (1938), *Arch. EntwMech. Org.*, **138**, 37.
BILLROTH, T. (1865), *Arch. klin. Chir.*, **6**, 372.
BORN, G. (1897), *Arch. EntwMech. Org.*, **4**, 517.
BORST, M. (1920), quoted by L. B. AREY, 1936.
BRUNST, V. V., and SCHEREMETJEWA (1933 a), *Roux Arch. EntwMech. Org.*, **128**, 181.
— — — — (1933 b), *Ibid.*, **130**, 771.
BURROWS, H. (1932), *Some Factors in the Localisation of Disease in the Body*. London: Baillière, Tindall & Cox.
BURROWS, M. T. (1924), *J. med. Res.*, **44**, 615.
CAMERON, G. R. (1952), *Pathology of the Cell*. London: Baillière, Tindall & Cox.
CARREL, A. (1910), *J. Amer. med. Ass.*, **55**, 2148.
— — (1912), *J. exp. Med.*, **15**, 516.
— — (1921), *Ibid.*, **34**, 425.
— — (1923), *Ibid.*, **36**, 385.
— — (1924), *C.R. Soc. Biol. Paris*, **90**, 333.
— — (1930), *Proc. Inst. Med., Chicago*, **8**, 62.
— — and BAKER, L. E. (1926), *J. exp. Med.*, **44**, 503.
— — and DU NOUY, L. (1921), *Ibid.*, **34**, 339.
— — and EBELING, A. H. (1923), *Ibid.*, **37**, 759.
— — — — (1926), *Ibid.*, **44**, 261.
— — and HARTMANN, A. (1916), *Ibid.*, **24**, 429.
CHALKLEY, H. W. (1943), *J. nat. Cancer Inst.*, **4**, 47.
— — ALGIRE, G. H., and MORRIS, H. P. (1946), *Ibid.*, **6**, 363.
CHILD, C. M. (1941), *Patterns and Problems of Development*. Chicago: University Press.
CLARK, E. R. (1936), *Ann. int. Med.*, **9**, 1043.
— — (1954), *Anat. Rec.*, **120**, 241.
— — and CLARK, E. L. (1932), *Amer. J. Anat.*, **51**, 49.
— — — — (1933 a), *Amer. J. Physiol.*, **105**, 19.
— — — — (1933 b), *Amer. J. Anat.*, **52**, 273.
— — — — (1936), *Biol. Bull.*, **71**, 405.
— — — — (1939), *Amer. J. Anat.*, **64**, 251.
— — — — (1944), *Anat. Rec.*, **88**, 426.
— — — — and ABELL, R. G. (1933), *Ibid.*, **55**, 50.
— — HITSCHLER, W. J., KIRBY-SMITH, H. T., REX, R. O., and SMITH, J. H. (1931), *Ibid.*, **50**, 129.
COE, W. R. (1929), *J. exp. Zool.*, **54**, 411.
CURTIS, W. C. (1936), *Biological Effects of Radiation*, Vol. 1, ed. B. M. Duggar. New York: McGraw-Hill.
DAVENPORT, C. B. (1934), *Coldspring Harbor Symposia*, **2**, 203.
DAVIDSON, M. E., and BERRILL, N. J. (1948), *J. exp. Zool.*, **107**, 465.
DU NOUY, L. (1936), *Biological Time*. London: Methuen.
EBERT, R. H., and FLOREY, H. W. (1939), *Brit. J. exp. Path.*, **20**, 342.
— — — — and PULLINGER, B. D. (1939), *J. Path. Bact.*, **48**, 79.
— — SANDERS, A. G., and FLOREY, H. W. (1940), *Brit. J. exp. Path.*, **21**, 212.
EBERTH, C. J. (1891), *Internat. Beitr. z. wissensch. Med.* (Festschr. R. Virchow.), **2**, 75. Berlin: Hirschwald.
FAURÉ-FREMIÈT, E., and VLÈS, F. (1919), *C.R. Acad. Paris.*, **168**, 363.
FISCHER, A. (1925), *Arch. exp. Zellforsch.*, **1**, 369.
FLOREY, H. W. (1954), *Lectures on General Pathology*. London: Lloyd-Luke.
GOODWIN, P. A. (1946), *Growth*, **10**, 75.
GRAY, J. (1929), *J. exp. Biol.*, **6**, 248.
HADFIELD, G. (1951), *Ann. R. Coll. Surg. Engl.*, **9**, 397.
HARABATH, R. (1928), *Virchows Arch.*, **268**, 794.
HARRIS, H. (1955), *Brit. J. exp. Path.*, **36**, 115.
HEIDENHAIN, M. (1923), *Arch. EntwMech. Org.*, 32.
HENSHAW, P. S., and MEYER, H. L. (1943), *J. nat. Cancer Inst.*, **4**, 351.
HOLMES, S. J. (1914), *J. exp. Zool.*, **17**, 281.
HORN, E. C. (1942), *J. Morph.*, **71**, 185.
KLEBS, E. (1875), *Arch. exp. Path. Pharmak.*, **3**, 124.
KORSCHELT, E. (1927), *Regeneration and Transplantation*, **1**. Berlin: Borntraeger.
LEVANDER, G. (1945), *Nature, Lond.*, **155**, 148.
LEWIS, W. H. (1931), *Bull. Johns Hopk. Hosp.*, **48**, 242.
LOEB, L. (1898), *Arch. EntwMech. Org.*, **6**, 297.
— — (1920), *J. med. Res.*, **41**, 247.
LUMIERE, A. (1917), *Rev. Chir. Paris*, **53**, 656.
— — (1918), *Ibid.*, **55**, 168, 549.
MEDAWAR, P. B. (1945), *Brit. med. Bull.*, **3**, 684.
— — (1947), *Essays on Growth and Form*, ed. W. E. Le Gros Clark, and P. B. Medawar. Oxford: Clarendon Press.
MELCHIOR, E., and ROSENTHAL, F. (1920), *Berl. klin. Wschr.*, **57**, 293.
MINERVINI (1904), *Virchows Arch.*, **175**, 238.
MINOT, C. (1908), *The Problem of Age, Growth and Death*. London: Pitman.
MORGAN, T. H. (1901), *Regeneration*. New York: Macmillan.
NEEDHAM, A. E. (1952), *Regeneration and Wound Healing*. London: Methuen.
NEEDHAM, J. (1936), *Order and Life*. Cambridge: University Press.
NETTLESHIP, A. (1943), *Amer. J. clin. Path.*, **13**, 349.
OPPEL, A. (1912), *Arch. EntwMech. Org.*, **35**, 371.
POYNTER, C. W. M. (1919), *Anat. Rec.*, **16**, 1.
RICHARDS, O. W. (1928), *J. gen. Physiol.*, **11**, 525.
— — and KAVANAGH, A. J. (1947), *Essays on Growth and Form*, ed. W. E. Le Gros Clark, and P. B. Medawar. Oxford: Clarendon Press.
ROBERTSON, T. B. (1923), *Chemical Basis of Growth and Senescence*. Philadelphia: Lippincott.
ROSE, S. M. (1948), *J. exp. Zool.*, **108**, 337.
SANDERS, A. G. (1955), personal communication.
— — EBERT, R. H., and FLOREY, H. W. (1940), *Quart. J. exp. Physiol.*, **30**, 201.
SANDISON, J. C. (1928), *Amer. J. Anat.*, **41**, 447, 475.
— — (1931), *Anat. Rec.*, **50**, 355.
SPAIN, K. C., and LOEB, L. (1916), *J. exp. Med.*, **23**, 107.
SPALLANZANI (1787), quoted by L. DU NOUY, 1936.
STEARNS, M. L. (1939), *Anat. Rec.*, **73**, Suppl. p. 49.
— — (1940 a), *Amer. J. Anat.*, **66**, 133.
— — (1940 b), *Ibid.*, **67**, 55.
THOMPSON, D'A. W. (1942), *On Growth and Form*. Cambridge: University Press.

THORNTON, C. S. (1949), *J. Morph.*, **84**, 459.
UMANSKI, E. (1938), *Bull. Biol. Med. exp. U.S.S.R.*, **6**, 141.
VAN DEN BRENK, H. A. S. (1955), *Int. Congr. Radiobiol.* (In the press.)
WERNER, R. (1902), *Beitr. klin. Chir.*, **34**, 1.
WIGGLESWORTH, V. B. (1937), *J. exp. Biol.*, **40**, 364.
— — (1947), *Essays on Growth and Form*, ed. W. E. Le Gros Clark and P. B. Medawar. Oxford: Clarendon Press.
WILBUR, K. M., and CHAMBERS, R. (1942), *J. exp. Zool.*, **91**, 287.
WILLIAMS, R. G. (1954), *Internat. Rev. Cytol.*, ed. G. H. Bourne and J. F. Danielli, **3**, 359.
WILLMER, E. N. (1947), *Essays on Growth and Form*, ed. W. E. Le Gros Clark, and P. B. Medawar. Oxford: Clarendon Press.
WOLFF, E., and DUBOIS, F. (1947), *Soc. Biol. Strasbourg*, **141**, 903.
WOODGER, J. H. (1947), *Essays on Growth and Form*, ed. W. E. Le Gros Clark, and P. B. Medawar. Oxford: Clarendon Press.
YOUNG, J. S., FISHER, J. A., and YOUNG, M. (1941), *J. Path. Bact.*, **52**, 225.

SHORT NOTES OF RARE OR OBSCURE CASES

NEUROBLASTOMA OF THE ADRENAL PRESENTING WITH INTRAPERITONEAL HÆMORRHAGE

BY B. J. S. GROGONO
FORMERLY SURGICAL REGISTRAR, PADDINGTON GENERAL HOSPITAL

INTRAPERITONEAL hæmorrhage is a well-known accompaniment of injuries to the liver, spleen, kidneys, and other abdominal viscera. It may also occur spontaneously as a complication of a variety of diseases such as ectopic gestation, ovarian cyst, uterine fibroids, aneurysms of the abdominal aorta or other abdominal arteries, glandular fever, acute pancreatitis, or hæmorrhagic diseases. Apart from the last-named, these conditions are seldom encountered in childhood. The following is therefore perhaps of some interest in that it concerns a young boy who presented with intraperitoneal hæmorrhage which was at first thought to be due to injury to the spleen, but later shown to be the result of trauma to a neuroblastoma of the adrenal gland.

CASE REPORT

HISTORY.—M. M., a boy aged 7½ years, was admitted to Paddington General Hospital on Oct. 10, 1953, complaining of left-sided abdominal pain. During play that morning he had knocked the left side of his abdomen on a piece of wood. He was able to walk home but was admitted to hospital two hours later suffering considerable pain. Closer questioning of the mother revealed that he had complained of episodes of abdominal pain for some weeks, but had continued attending school.

ON EXAMINATION.—The patient was pale and drowsy and lay on his left side with his knees flexed, pulse 110, blood-pressure 110/60, temperature 97° F. There was considerable tenderness and muscle rigidity in the left upper abdomen. No shoulder pain was present and no shifting dullness could be demonstrated in the abdomen. It was noticed that the left eye was unduly prominent.

A plain X-ray examination of the abdomen and chest showed the heart and lungs to be normal; the stomach gas shadow was displaced a little to the left.

DIAGNOSIS AND TREATMENT.—A provisional diagnosis of intracapsular injury to the spleen was made and the child was kept under careful observation. During the next few hours, however, his pulse remained rapid, the pain became more severe, and he commenced to vomit. In view of this unfavourable response it was felt that the only safe course was to carry out an exploratory laparotomy.

AT OPERATION.—On opening the abdomen by a left paramedian incision a considerable quantity of blood was found in the peritoneal cavity. However, this was seen to be derived not from the spleen, which was normal, or from a small neighbouring splenuculus, but from rupture of a large retroperitoneal hæmatoma into the peritoneal cavity. This hæmatoma occupied most of the posterior abdominal wall of the left half of the abdomen. The abdominal wound was enlarged by a transverse extension across the left rectus muscle, and the splenic flexure and transverse colon were displaced medially to allow the hæmatoma to be explored. When this was done it was found that a large encapsulated tumour was present at the upper pole of the left kidney and that the hæmorrhage had arisen from this tumour. A left nephrectomy was

FIG. 653.—Macroscopical appearance. Hæmorrhage tumour attached intact left kidney (operation specimen).

performed, removing the kidney and the neoplasm. The retroperitoneal space was drained through a stab wound in the left flank and the wound was closed. One pint of blood was given during the operation.

PATHOLOGICAL REPORT (Professor Newcomb).—The tumour is separate from the kidney, but involves the adrenal. It is hæmorrhagic and consists of masses of small cells with darkly stained nuclei. Although no rosettes have been demonstrated it is most probably a neuroblastoma. (*Figs.* 653-655.)

PROGRESS.—The boy made an entirely uneventful immediate recovery from the operation and was discharged to a Convalescent Home on Oct. 31. His appearance on Dec. 31 is shown in *Fig.* 656. It will be noted that the eyes are slightly prominent, but radiological examination of the skull at this stage showed no evidence of bony metastases.

On Jan. 15, 1954, he was re-admitted with headache and vomiting. Examination showed that he was thin, pale, and ill. There was marked proptosis affecting the left eye more than the right. Blue discoloration of the orbital margin was apparent but there was no ophthalmoplegia. Two small bony swellings were felt in the frontal and fronto-parietal regions of the skull. Hard lymph-nodes could be palpated in both axillæ and in the right groin and were indeed visible in the latter situation (*Fig.* 657). The lower edge of the liver was percussable two fingerbreadths below the costal margin in the right

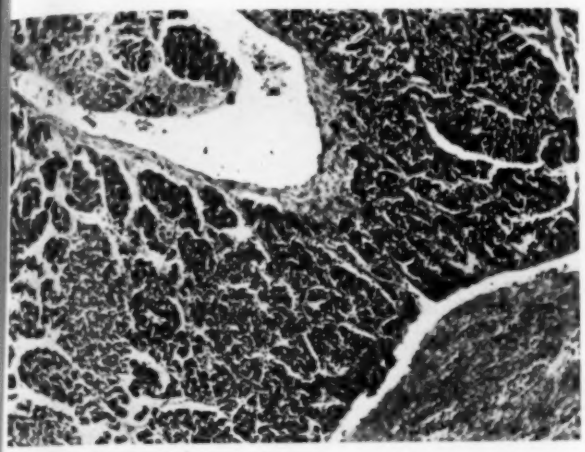


FIG. 654.—Microscopical appearance. *Right*, an organizing hæmorrhage; *Left*, a vessel containing 'malignant embolus'. (× 40.)

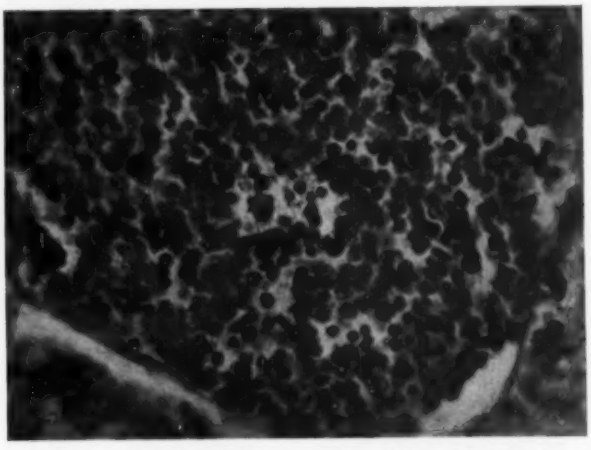


FIG. 655.—Microscopical appearance. Cells with vesicular nuclei and scanty cytoplasm. (× 180.)

FIG. 656.—Appearance seven weeks after operation.

FIG. 657.—Appearance three months after operation.

nipple line. His hæmoglobin was 46 per cent and E.S.R. 46 mm./hr. Radiological examination showed unmistakable evidence of extensive metastatic deposits in the skull and a pathological fracture in the fourth right rib.

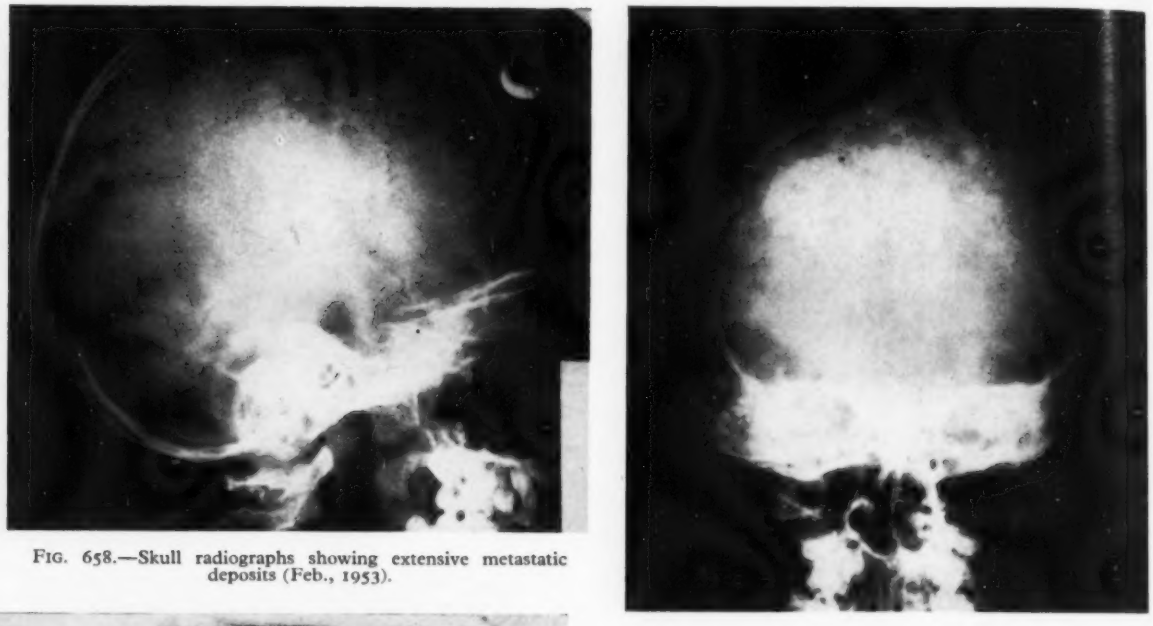


FIG. 658.—Skull radiographs showing extensive metastatic deposits (Feb., 1953).

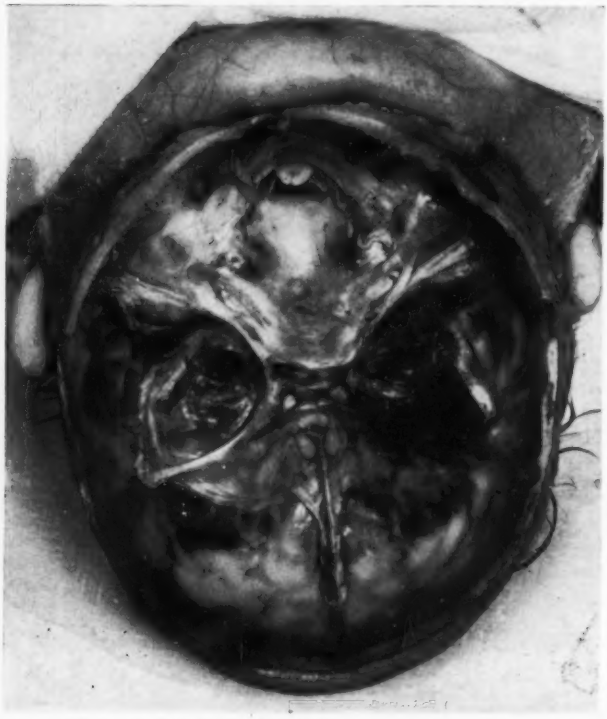


FIG. 659.—Autopsy specimen. Dark hæmorrhagic infiltration of middle and anterior fossæ, involving dura and skull, but not brain.

Examination of the central nervous system revealed no abnormality apart from a suggestion of papillœdema in the left optic disk.

In view of the marked anæmia and widespread nature of the disease it was decided, after consultation with Dr. M. Hulbert, Director of the Radiotherapy Department of St. Mary's Hospital, to withhold irradiation until localized symptomatic treatment was indicated. At Dr. R. Lightwood's suggestion a course of vitamin B_{12} 100 μg for three days was given. The rapid downward course continued. As the general condition deteriorated so the metastatic deposits became more apparent, and a left-sided headache gave increasing discomfort. Extensive secondary deposits were now present in the skull (*Fig.* 658), ribs, liver, and lymph-glands. The lungs, however, remained clear. Proptosis became so severe as to threaten dislocation of the left eye, though sight remained and he continued to take an active interest in his fellow patients and surroundings. A course of radiotherapy was given to the skull to try to diminish the proptosis and headache and to provide some terminal relief.

On Feb. 24 sciatic pain and a foot drop developed on the left side. A swelling was noted in the left lumbar region.

On Feb. 26 the patient died.

NECROPSY FINDINGS (Dr. Caplin).—

Conclusion and Cause of Death.—Secondary carcinomatosis (primary neuroblastoma (L) adrenal).

Summary of Post-mortem Findings.—Thin lad, bilateral proptosis.

Skull: Multiple deposits of hæmorrhagic tissue in calvarium and base of skull and orbits. Dura studded with multiple nodules (*Fig.* 659). *Brain*: Œdematous but no intracerebral deposits.

Thorax: All ribs include extensive hæmorrhagic tumour deposits largest being to fourth rib posteriorly—forming an intrathoracic tumour up to 4 cm. diameter.

Lungs: Pale and œdematous. No secondaries.

C.V.S.: Nil.

Abdomen: Fibrous adhesions related to healed laparotomy scar.

Stomach and intestines: Free from growth. Liver large, pale, and fatty, with multiple tumour deposits up to 1 cm. in size.

Gall-bladder and pancreas: Nil.

Spleen: Some infradiaphragmatic N.G. deposits, joining spleen to diaphragm.

Left kidney and adrenal: Absent—replaced by large nodular purplish-white mass adherent to peritoneum.

Right kidney and suprarenal: Normal.

Lymphatic glands: Paraortic lymph-glands extending from diaphragm to pelvis and ileum, and inguinal also grossly enlarged and replaced by tumour.

HISTOLOGICAL REPORT.—
1, 2. Secondary neuroblastoma, with new-bone formation in skull (*Fig.* 658) and orbital plate.
3. Secondary in portal vein and sinusoids in liver.
4. Secondary in mediastinum.
5. Secondary in abdominal lymphatic gland.
6. Secondary in diaphragm.
7. Normal right suprarenal.

DISCUSSION

Intraperitoneal hæmorrhage is a rare mode of presentation of neuroblastoma of the adrenal gland. It is not mentioned in a review of 600 cases of this disease by Philips (1953), who found that the diagnosis in the early stages was usually very difficult because the symptoms were often intermittent and non-specific.

In the case described, only after repeated questioning was a rather vague history of malaise and abdominal pain elicited. A definite story of injury led to confusion with a traumatic rupture of the spleen which was only dispelled by exploratory laparotomy.

Although this case followed the fatal pattern so familiar in cases of neuroblastoma, a temporary improvement followed excision of the tumour, and led to the hope of spontaneous remission one month after operation. When metastases did occur they were widespread and rapidly growing. Profound anæmia and severe proptosis were marked features.

Spontaneous regression of similar deposits have been described :—

1. Without specific treatment (Gross, 1953) ;
2. After removal of the primary tumour, in part or complete ;
3. After X-ray therapy (Lehman, 1952) ;
4. Following treatment with massive doses of vitamin B_{12} ;
5. Transformation into ganglioneuroma.

SUMMARY

A case is reported of neuroblastoma of the adrenal presenting with intraperitoneal hæmorrhage, possibly excited by an injury to the loin. The course of the disease before and after removal of the tumour is described. Vitamin B_{12} in large doses produced no remission. The post-mortem findings confirmed extensive deposits in the skull, dura, lymphatics, and liver.

I would like to thank Professor J. C. Goligher for assistance in publishing this case ; Dr. Caplin for the autopsy report ; Dr. Salmon for the photomicrographs ; and Dr. P. N. Cardew, of the Photographic Department of St. Mary's Hospital, for the other photographs.

BIBLIOGRAPHY

CUSHING, H., and WOLBACH, S. B. (1927), *Amer. J. Path.*, **3**, 203.
GROSS, R. E. (1953), *Surgery of Infancy and Childhood*, 606–625. Philadelphia and London : W. B. Saunders Co.
KARSNER, H. T. (1950), *Atlas of Tumours of the Adrenal*, 29–35. Washington : Armed Forces Institute of Pathology.
LEHMAN, E. P. (1952), *Ann. Surg.*, **95**, 473.
PHILIPS, R. (1953), *Ann. R. Coll. Surg. Engl.*, **12**, 29.
POORE, T. N., DOCKERTY, M. B., KENNEDY, R. L. J., and WALTERS, W. (1951), *Surg. Clin. N. Amer.*, **31**, 1121.
SPINK, M. S. (1954), *Lancet*, **2**, 144.

TRAUMATIC RUPTURE OF HEPATIC DUCT

BY JOHN A. BATY, SHREWSBURY

IN all, about 50 cases of subparietal rupture of the bile-ducts have been reported in the literature, and in this number invariably the common duct appears to have been involved. Since Rudberg (1921) recorded a case of injury to the common duct and reviewed another 40 cases, Edlington (1933) described a single case of traumatic rupture of the bile ducts and Lewis (1938) gave details of a further case with review of 6 additional cases. The only cases reported since then were of complete rupture of the common duct (Lysaght, 1939), injury to common duct and pyloric antrum (Grimault, 1947), and a tear near the junction of hepatic ducts (Milnes Walker, 1953). Details are now recorded of a case in which extrahepatic injury was limited to the left hepatic duct.

CASE REPORT

A well-built man, aged 25, was admitted to the Royal Salop Infirmary shortly after having been crushed between the back of his lorry and a wall. The patient's back had been forced against the wall and the impact of the vehicle had caught him across the front of the right lower chest. There was no break in the skin and the patient did not appear pale or unduly shocked. B.P. 130/80. He complained of pain across the lower chest and down the right side of the abdomen, where guarding was present. Some respiratory distress was noted but the thoracic cage was intact and no abnormality could be found in the chest. Within an hour of admission, the pulse-rate had risen from 112 to 120, the abdominal pain and rigidity had increased, bowel sounds were faint, and there was tenderness in the rectovesical pouch. Rupture of the liver was diagnosed and transfusion commenced.

FIRST OPERATION.—This was carried out on Sept. 24, under pentothal, flaxedil, and cyclopropane anæsthesia (Dr. Polland). The abdomen was opened through a right upper paramedian incision in order to evacute a large quantity of blood and clot. A systematic exploration revealed no visceral damage other than to the liver. In this organ there were several non-bleeding splits, together with a deep laceration parallel with the medial side of the gall-bladder bed extending towards the porta hepatis. Active bleeding from this laceration was controlled by a series of deep catgut sutures tied over gelatin sponge. There was no evidence of any bile leakage and the abdomen was closed with a stab drain in position down to Morrison's pouch.

PROGRESS.—The patient's condition appeared quite satisfactory immediately after the laparotomy and flatus was passed on the third post-operative day. Within

twenty-four hours, there was a free drainage of bile from the stab incision, the quantities diminishing to no loss by the seventh day: the stab drain was removed on the tenth post-operative day and the stitches on the twelfth day. Meantime, normally coloured motions were being passed daily. The temperature had risen to 101° F. on two occasions, but with procaine penicillin, 200,000 units, 6-hourly for ten days, the patient was afebrile by the thirteenth day. At the beginning of the third week a swinging pyrexia returned. Although the patient did not look so well, he had no definite complaint until diarrhœa for twenty-four hours was accompanied by a feeling of abdominal distension. On the next day, bile appeared in the urine and, within twenty-four hours, the stools were clay-coloured. Radiographs taken after biligrafin failed to outline the biliary ducts, but revealed a collapsed gall-bladder. At this stage increasing distension of the abdomen was associated with vague discomfort, but no actual pain. Rigidity was absent and bowel sounds were present in all quadrants. The conjunctivæ were clear of icteric tinge, but this showed itself during the short pre-operative course of vitamin K.

SECOND OPERATION.—On Oct. 19, under pentothal, flaxedil, nitrous oxide, oxygen, trilene, and pethidine anæsthesia (Dr. Zair). The previous incision was opened up and extended in both directions. Many pints of bile were evacuated and bile-stained œdematous omentum was freed from the structures in the upper right quadrant. A free-lying elongated portion of tissue was lifted out from the region of the previous repair to expose an unhealed cleft in the liver. Difficulty was encountered from the bile-stained œdematous tissues of the lesser omentum, but a normal-sized common bile-duct was exposed and followed upwards. Bile was being liberated as the swollen fat was eased, and eventually a pocket was opened up to expose a longitudinal laceration of the left hepatic duct. Having opened the common bile-duct between stay sutures, an attempt was made to introduce one limb of a T-tube up to the region of the tear, but it could not be coaxed beyond the junction of right and left hepatic ducts. One had to be content with a shorter T-tube anchored in the common bile-duct. Using fine catgut on a small eyeless needle, some four to five sutures were inserted to close the aperture in the left hepatic duct. After bringing the T-tube out in the midline, the abdominal wound was closed with a series of figure-of-eight nylon sutures and a stab drain inserted down to Morrison's pouch. During the operation the patient received 2 pints of blood and he returned to the ward with an intravenous drip of Hartmann's solution, which was continued for forty-eight hours.

PROGRESS.—Within twelve hours there was free drainage along the T-tube and rapid diminution of bile leakage from the stab drain. Between the fourth and twelfth day, each 24 hours, a pint of bile was drained and returned rectally. At the end of a week the blood chemistry was as follows: Chloride 86 (500 mg./100 ml.); bicarbonate 27 (61 ml. CO_2/100 ml.); sodium 113 (260 mg./100 ml.); urea 35 mg./100 ml.

Enemata on alternate nights produced flatus, and a clay-coloured motion was passed on the seventh post-operative day. From the tenth day there was a steady reduction in the drainage from the T-tube and by the twelfth day the motions were of normal colour. The daily quantities of bile from the T-tube were as follows: 20, 16, 14, 14, 10, 8, 4, 2, 1 oz. The stab drain along which there had been no leakage after five days was retained until the fifteenth day. At this stage a cholangiogram showed that the T-tube was no longer in the common bile-duct and it was therefore removed. Radiography after biligrafin revealed that the gall-bladder was filling in a satisfactory manner, but the ducts were not outlined. The patient was discharged from hospital on Nov. 11, free from symptoms and with the wound firmly healed.

On May 3, 1955, eight months after the injury, the patient reported again to request permission to play football. He had put on at least 1 st. in weight and was carrying on his ordinary work as a lorry driver, completely free from all symptoms.

The laparotomy scar was sound, without any trace of yielding. Opportunity was taken to have a further biligrafin examination: This showed a normal gall-bladder and a left hepatic duct without stenosis.

DISCUSSION

The mechanism which produces extrahepatic duct injury is invariably the same, a crushing trauma involving the upper right abdomen and the lower right chest: some vehicle is the usual factor responsible. Lewis (1938) assumed that bile-duct injury was produced by a force applied in such a direction as to crush the ducts between the liver and the bodies of the vertebræ. In the present case much of the effect of the trauma was sustained by the liver itself, and maybe one of the lacerations produced by liver compression extended onwards into the left hepatic duct. It is possible that the hepatic ducts were unusually long and, whilst this factor rendered them more liable to damage, it made repair an easier matter.

In many of the cases described, exploration has been delayed for varying reasons until a number of days after the accident; the cardinal signs of bile-duct injury—namely, increasing fluid in the abdomen, jaundice, and clay-coloured stools—have eventually led to the necessary laparotomy. Unfortunately, in the case reported, at the early exploration, no free bile was seen and attention was not directed towards the ducts. With an intact right hepatic duct progress appeared satisfactory, the stab drain leakage ceasing in a few days and the stools being normal coloured. Meantime the torn left hepatic duct continued to drain into the peritoneal cavity and it is surprising there was no complaint of pain and little of constitutional upset. Instead of the cardinal signs appearing in three days, as has usually been noted, they were delayed for over two weeks. It is likely that the accumulation of many pints of bile in the peritoneal cavity, combined with the overplastering of œdematous fat, produced external pressure on the common bile-duct: only then did clay-coloured stools appear and bile show itself in the urine.

It is unlikely that biligrafin has previously been employed in connexion with bile-duct injury. Hicken and Stevenson (1948) injected diodrast into a collapsed gall-bladder found at operation and they were able to demonstrate a laceration on the postero-medial wall of the common bile-duct. By the time that further laparotomy was decided upon in the case reported, support to the diagnosis of duct injury was given by biligrafin administration, which demonstrated a collapsed gall-bladder. Later, biligrafin showed satisfactory refilling of the gall-bladder and, eight months after the injury, it was used to demonstrate that the left hepatic duct was free from stenosis.

Lewis suggests that repair of a rupture of the hepatic duct is usually technically impossible owing to its inaccessibility. Although in the present case it was possible to suture the left hepatic duct, biliary decompression would appear to be the all-important factor in promoting healing of the tear. It is stated

that most lacerations heal spontaneously without the necessity for repair provided provision is made for continuous decompression.

SUMMARY

A case of rupture of the left hepatic duct is described.

Clinical findings and treatment are discussed.

Biligrafin examination is employed for the first time in a case of this type.

REFERENCES

EDLINGTON, G. H. (1933), *Brit. J. Surg.*, **20**, 679.
GRIMAULT, M. L. (1947), *Mém. Acad. Chir.*, **73**, 205.
HICKEN, N. F., and STEVENSON, V. L. (1948), *Ann. Surg.*, **128**, 1178.
LEWIS, K. M. (1938), *Ibid.*, **108**, 237.
LYSAGHT, A. C. (1939), *Brit. J. Surg.*, **26**, 646.
RUDBERG, H. (1921), *Münch. med. Wschr.*, **68**, 1680.
WALKER, J. H. MILNES (1953), *Lancet*, **2**, 969.

FISHBONE PERFORATION OF MECKEL'S DIVERTICULUM

BY J. K. M. RAWLINSON

REGISTRAR, BIRKENHEAD GENERAL HOSPITAL

IN a recent review of foreign-body perforations of Meckel's diverticulum (Alhadeff, 1955) only 27 cases are recorded from a survey of literature dating back to 1899; 16 of these were by a fishbone. Another case of a fishbone perforation of Meckel's diverticulum is reported here. This presented an acute abdominal emergency, and the signs and symptoms were so suggestive that the correct diagnosis was seriously considered before operation.

CASE REPORT

The patient, a chief steward, aged 57 years, was admitted to the casualty department at 12.30 p.m. on May 15, 1954, and there diagnosed as acute appendicitis. When seen 1½ hours later, he described how, during that morning while walking in the street, he had experienced the sudden onset of severe abdominal pain which doubled him up. Pain was generalized over the whole abdomen, but felt most in the umbilical area; it was not of a colicky nature, was not associated with nausea or vomiting, and was not relieved by passing wind. There was no history of any injury or strain. The severe pain, which at one time passed through to the back, was present for about two hours and then became easier. It returned just before admission, being felt in the right iliac fossa, mainly just below and to the right of the umbilicus. An hour and a half after admission pain was still present in the right iliac fossa, although it was not so severe as before; it was aggravated by any movement. He had not vomited and had no nausea, although he professed no interest in food. His appetite was usually good, he could eat anything, and did not suffer any indigestion. His bowels moved regularly once daily and he had had a normal bowel action that morning, passing no blood or mucus. Micturition was normal, and his weight steady. He had had no serious illnesses in the past.

ON EXAMINATION.—He was a healthy looking, well-nourished man of good colour. Temperature 97·8°, pulse 88, respirations 20. His tongue was clean. He was tender over the whole of the right side of the abdomen, including the umbilical area, but maximally in the right iliac fossa 1½ in. nearer to the umbilicus than McBurney's point. Rebound tenderness was present, but there was no guarding or rigidity, no distension, and nothing abnormal palpable. Bowel sounds were present and not exaggerated, and hernial orifices were intact. Rectal examination revealed slight tenderness high up on the right side in the rectovesical pouch.

Although clinical examination was suggestive of acute appendicitis, the history was so far from being typical and the signs so diffuse that it was decided to keep him under observation for a short time.

Three hours later, his pulse-rate was still 88–90; symptoms and signs were the same as before except that rebound tenderness was more marked, and there was guarding in the right iliac fossa. It was therefore decided to carry out a laparotomy with a doubtful diagnosis of acute appendicitis; the possibility of a perforated or inflamed Meckel's diverticulum was considered quite likely in view of the history and the signs, particularly the point of tenderness.

FIG. 660.—Showing the Meckel's diverticulum with the protruding fishbone.

AT OPERATION.—The abdomen was opened through a right paramedian incision. There was a small amount of turbid free fluid. The appendix was bound down at its proximal end by adhesions but was not inflamed. The lower ileum was examined, and a Meckel's diverticulum 1 in. long by ¾ in. in diameter was found, with the tip acutely inflamed and perforated by a needle-like fish bone 1 in. long which was protruding for ¾ in. (*Fig.* 660). A small mesentery containing an artery was present, running from the mesentery proper of the ileum alongside the bowel to the base of the diverticulum. This mesentery was ligated and divided. The diverticulum was excised at its base, the resulting defect being closed transversely in two layers.

The appendix was removed and the abdomen closed without drainage.

POST-OPERATIVE COURSES.—He was given streptomycin ½ g. b.d. and only water by mouth for 48 hours. His convalescence was uninterrupted apart from the discharge of a small amount of blood-stained serum from the wound on the fourteenth day. This cleared up in three days and he was discharged on June 3.

He was seen again on June 25 and was free from symptoms. He was discharged to light duties.

On subsequent questioning, he could not be positive about the date of his last fish meal, but was certain that it was at least one week prior to his admission.

DISCUSSION

Diagnosis.—The diagnosis of a diseased Meckel's diverticulum is always difficult, can rarely be certain and is usually made at operation, having been unsuspected clinically. In retrospect there are several interesting features about this case. The onset of the pain—sudden, severe, and not of a colicky nature—and the complete absence of previous symptoms suggested some acute peritoneal irritation such as perforation. (A perforated appendix nearly always presents the symptoms of inflammation before the perforation, and the moment of perforation is often followed by a temporary relief of symptoms.) The reference of the pain to the umbilical area implied lower ileum not in contact with parietal peritoneum. While tenderness over McBurney's point is not constant in appendicitis, it is found in the great majority of cases and is often remarkably well localized. The tenderness here was above and medial to McBurney's point close to the umbilicus, an uncommon point of tenderness in acute appendicitis ; in actual fact this was the approximate position of the diverticulum. When examined three hours or so after the perforation when local peritonitis, although mild, was present, rebound tenderness was noted ; in the writer's experience this sign has nearly always been of great significance, indicating local or general peritonitis. Three hours later this suspicion of peritonitis was increased by the development in the intervening period of guarding. There was a clear indication for laparotomy, and, bearing these points in mind, it was justifiable to doubt the diagnosis of acute appendicitis and to consider some abnormality, probably perforation, in the lower ileum, possibly in a Meckel's diverticulum.

The sudden onset of severe symptoms here described does not accord with the findings of Seibert (1950), or of Persson (1939), who state that symptoms are usually mild and not those characteristic of perforation. All reviews agree that Meckel's diverticulum is found two to four times more often in men than in women, but 90 per cent of subjects with symptoms arising from disease of a Meckel's diverticulum are under 30 years of age (Jay, Margulis, McGraw, and Northup, 1950). In the case under discussion the patient was aged 57 years.

While the presence of foreign bodies in a Meckel's diverticulum is relatively common, probably owing to the wide neck which is usually present, perforation by foreign body is rarely encountered. Ward-McQuaid (1950) suggests that the mechanism of perforation is partly the local inflammation produced by irritation and stagnation of the foreign body, and partly a pressure necrosis of the overlying wall of the diverticulum consequent upon the repeated attempts by peristalsis to pass the object onwards towards the tip of the diverticulum. This is unlike the mechanism of perforation of the appendix, which is either secondary to local gangrene of the appendix wall following (infective) thrombosis of its vessels, or the result of increased pressure within the lumen of the inflamed appendix after its proximal end has become obstructed by œdema or a foreign body. This patient was certain that no fish had been eaten for at least a week previous to his admission. In view of the usually rapid passage of ingested foreign bodies through the stomach and small bowel, it is quite likely that this fish bone had been in the diverticulum for six to seven days at least, giving ample time for the local tissue changes leading up to perforation as mentioned above, to take place. Jay and others (1950) give three criteria for the recognition of a Meckel's diverticulum, one of which is that it should have its own blood-supply running in a small mesentery which extends outwards to the base of the diverticulum from the mesentery of the ileum. In the author's experience of 5 cases this small mesentery has been present every time.

The importance of a routine search for a Meckel's diverticulum, particularly when doing a gridiron appendicectomy, has been stressed by many surgeons, including Sibley (1944), Wagner, Shallow, and Eger (1950), and Macfarlane (1948). The diverticulum has an overall incidence of 1–4 per cent, and it is estimated that 15–20 per cent of diverticula give rise to pathological symptoms (Christie, 1931) although this estimate may be too high (Moses, 1947). Cases are reported where the abdomen has been opened for appendicitis and a normal appendix found and removed ; at a second operation a pathological Meckel's diverticulum was removed, the patient's life having been seriously endangered in the meantime (Christensen, 1954 ; Whelan, 1951 ; Jay and others, 1950). Occasionally a diseased diverticulum exists together with an acutely inflamed appendix, and appendicectomy without removal of the diverticulum has been followed by the death of the patient (Aalkjaer, 1937, quoted by Christensen, 1954). Succeeding generations of medical students repeat that the diverticulum is usually 2 in. long, found in 2 per cent of cases, and is situated 2 ft. from the ileocæcal valve. It is not commonly realized, however, that the majority of diverticula occur proximal to this. Jay and others (1950), in a review of 103 cases, found that 4 per cent lie within 6 in., 28 per cent within 18 in., and 72 per cent within 36 in. of the ileocæcal valve ; 28 per cent therefore are found at a point more than 36 in. proximal to the ileocæcal valve, and in one case this distance was 66 in. It is recommended therefore that 5 ft. of the ileum proximal to the ileocæcal valve should be inspected.

Treatment.—Simple ligature of the base with purse-string invagination as for appendicectomy is condemned, because heterotopic tissue (usually gastric in type), when present, is usually found at the base ; simple ligature will probably leave some of this tissue behind and further complications will follow (Watt and Timpone, 1940).

With the affected loop of ileum isolated by clamps, the diverticulum should be excised at the base, the resultant defect being closed in a transverse axis with two layers of sutures. An aseptic method of resection and closure is ideal, although the open method can usually be satisfactorily and safely accomplished. Occasionally the adjacent bowel is so affected by the disease that simple resection and suture is impossible ; or the bowel may be narrowed, usually just distal to the diverticulum, so that there is a danger of producing obstruction by resection. In such cases, the short length of ileum containing the diverticulum

should be excised, continuity being restored by end-to-end anastomosis.

In the author's experience of 5 cases (3 incidental findings—'normal' diverticula, 1 fishbone perforation, and 1 diverticulum with multiple secondary diverticula arising from it) simple resection with closure in a transverse axis was carried out in 4 cases. In the fifth (diverticulum with multiple secondary diverticula) the bowel was markedly narrowed just distal to the diverticulum, and resection of 4 in. of bowel, including the diverticulum, with end-to-end anastomosis, was carried out. There were no deaths.

Mortality.—The fact that disease of a Meckel's diverticulum can be fatal in a relatively high proportion of cases is probably influenced by the difficulties of diagnosis. Wagner, Shallow, and Eger (1950) had 3 deaths out of 19 cases of diseased Meckel's diverticulum (15·8 per cent); on the other hand, mortality following the removal of a diverticulum found incidentally and not diseased, is practically nil; a further point strongly in favour of the routine search for its presence during appendicectomy, and its removal wherever possible.

SUMMARY

1. A case of Meckel's diverticulum perforated by a fishbone, where the diagnosis was considered preoperatively is described.

2. From a review of the literature several outstanding points in the clinical history and treatment are considered.

3. A renewed plea for the routine search for a Meckel's diverticulum, and its removal when possible, is made, and the importance of inspecting bowel for at least 5 ft. proximal to the ileocæcal valve is stressed.

I wish to thank Mr. J. B. Oldham for permission to publish this case, and to acknowledge the help which he and Mr. Frank Evans have given me in the preparation of this paper.

BIBLIOGRAPHY

AALKJAER, V. (1937), *Hospital Stidende*, **80**, 1219.
ALHADEFF, R. (1955), *Brit. J. Surg.*, **42**, 527.
CHRISTENSEN, E. (1954), *Brit. med. J.*, **1**, 1347.
CHRISTIE, A. (1931), *Amer. J. Dis. Child.*, **42**, 544.
CURD, H. H. (1936), *Arch. Surg., Chicago*, **32**, 506.
JAY, G. D., MARGULIS, R. R., MCGRAW, A. B., and NORTHUP, R. R., (1950), *Ibid.*, **61**, 158.
MACFARLANE, D. A. (1948), *Brit. J. Surg.*, **35**, 421.
MAYO, C. W. (1933), *Proc. Mayo Clin.*, **8**, 230.
MERRITT, W. H., and RABE, M. A. (1950), *Arch. Surg., Chicago*, **61**, 1083.
MOSES, W. R. (1947), *New Engl. J. Med.*, **237**, 118.
PERSSON, VON THORSTEN (1939), *Acta chir. scand.*, **82**, 530.
ROSSMAN, J. I. (1943), *Canad. med. Ass. J.*, **49**, 1.
SEIBERT, F. M. (1950), *Arztl. Wschr.*, **550**, 1023.
SHULLINGER, R. N., and STOUT, A. P., (1934), *Arch. Surg., Chicago*, **28**, 440.
SIBLEY, W. L. (1944), *Ibid.*, **49**, 156.
TAYLOR, S. (1947), *Lancet*, **2**, 786.
WAGNER, F. B., SHALLOW, T. A., and EGER, S. A. (1950), *Gastroenterology*, **16**, 539.
WARD-MCQUAID, J. N. (1950), *Lancet*, **1**, 349.
WATT, J. G., and TIMPONE, P. J. (1940), *Amer. J. Surg.*, **47**, 612.
WHELAN, P. J. (1951), *Canad. med. Ass. J.*, **64**, 67.
WOLFSON, W. L., and CLURMAN, M. J. (1930), *Ann. Surg.*, **92**, 388.

REVIEWS AND NOTICES OF BOOKS

New Concepts of Surgery of the Vascular System. By EMILE HOLMAN, M.D., Professor of Surgery, Stanford University School of Medicine, San Francisco, Cal. No. 27, *American Lecture Series*. 8½ × 5½ in. Pp. 108 + vi, with 47 illustrations. 1955. Springfield, Ill.: C. C. Thomas (Oxford: Blackwell Scientific Publications). 18s.

WE have come to expect a high standard of literary form and artistic production in the monographs which constitute the American Lecture Series, and it may be said at once that the two lectures by Professor Holman which are published in this little volume come well up to expectation. Surgeons who are specially interested in the vascular system are familiar with the substantial contributions he has made in the course of the past thirty years to our knowledge of the physiology, pathology, and surgery of the blood-vessels, and all will wish to add this valuable book to their libraries.

The first lecture, which was the first David W. Yandell Lecture to be delivered at the University of Louisville School of Medicine, deals with the immediate and late treatment of arterial injuries and provides an admirable summary of the advances in arterial surgery which were made during the Korean War, with an account of the special features in medical organization which made these advances possible. The most important points in the technique of exposure of the main arteries of the limbs and neck, and in methods of suture so as to avoid constriction of the line of anastomosis are clearly illustrated; and repeatedly one is reminded of Holman's own researches into the dynamics of the circulation in the neighbourhood of an arteriovenous fistula.

The second lecture, on post-stenotic dilatation as a factor in the development of arterial aneurysms, was the Arthur Dean Bevan Lecture to the Chicago Surgical Society in 1954, and includes a wealth of clinical and experimental observations dealing with the pressure effects in tubes beyond strictures, and with the structural fatigue which occurs in living tissue as well as in metals. It is a fascinating study presented in a literary style which makes the exposition of scientific argument a delight to the reader.

L'Anesthésie en Chirurgie thoracique. Évolution des Techniques; Les Méthodes et leurs Indications; Stastistique. By OLIVIER MONOD and others. With a Preface by Professor P. MOULONGUET. 8¾ × 5½ in. Pp. 120 + xii, with 6 illustrations. 1955. Paris: Masson et Cie. 850 fr.

THIS small book first describes the development of anæsthesia for thoracic surgery in a number of hospitals in France from the year 1933 up to the year 1954. In

this period of time, nearly 7000 operations of various types were performed. Anæsthetic techniques for various thoracic operations and the difficulties which may occur during operation are described. There is a chapter on anæsthesia for cardiac surgery and hypothermia is also considered in some detail; from their experiences, the authors consider that the advantages of this method outweigh its dangers and that it will be of value in cardiac surgery.

Peptic Ulcer. Diagnosis and Treatment. By CLIFFORD J. BARBORKA, M.D., M.S., D.Sc., F.A.C.P., Associate Professor of Medicine and Chief, Gastro-intestinal Clinics, Northwestern University Medical School; and E. CLINTON TEXTER, jun., M.D., Associate in Medicine and Assistant Chief, Gastro-intestinal Clinics, Northwestern University Medical School. $8\frac{3}{8} \times 5\frac{3}{8}$ in. Pp. 290 + xiii, with 33 illustrations. 1955. Boston and Toronto: Little, Brown & Co. (London: J. & A. Churchill Ltd.) 50s.

PEPTIC ulceration is a common condition which affects about 10 per cent of the population and if anything is on the increase. Much has been written about this common disease and yet much has yet to be discovered regarding its aetiology. This monograph gives a clear and concise description of the diagnosis and treatment of peptic ulcer, including the use of the anticholinergic drugs, their value in the acute attack, and their place in the management of the long-term ulcer problem.

A very useful appendix is to be found at the end of the book which is devoted to the recipes for foods commonly used in peptic ulcer management.

This little book gives the reader an up-to-date account of the diagnosis and treatment of a very common condition.

Standard Atlas of Human Anatomy. Descriptive and Regional. By M. W. WOERDEMAN, M.D., D.Sc., Professor of Anatomy and Embryology and Rector-President of the University of Amsterdam. $9\frac{7}{8} \times 6\frac{3}{8}$ in. Vol. I, Osteology, Arthrology, Myology. 512 illustrations; index. 1955. Amsterdam: Scientific Publishing Co. (London: Butterworth & Co. Ltd.). 72s. 6d.

THAT a third edition of this work was necessary within seven years speaks for itself and for the great popularity the book enjoys. Professor Woerdeman has added many new illustrations, all of which are of a very high standard. This present volume comprises the entire locomotor apparatus, combining osteology, arthrology, and myology. The nomenclature used is the B.N.A., which is up to now most generally accepted.

There can be little doubt that this standard atlas of human anatomy will long remain the reference volume not only for students, but for anatomists and surgeons as well.

An excellent production.

The Surgical Technic of Abdominal Operations. By JULIUS L. SPIRACK, M.D., LL.D., F.A.C.S., Associate Professor of Surgery, University of Illinois College of Medicine. Fifth edition. $9\frac{3}{4} \times 6\frac{1}{4}$ in. Pp. 931 + xx, with 495 illustrations. 1955. Springfield, Ill.: Charles C. Thomas (Oxford: Blackwell Scientific Publications Ltd.). 126s.

THE new fifth edition of this work has been very thoroughly revised and some one hundred and fifty-three new illustrations have been added, while many old and dated illustrations have been deleted. Illustrations play an important part in a volume such as this, and on the whole they are unusually well done, but why the author still wishes to illustrate operations for pyloroplasty, gastropexy, and gastroduodenostomy is hard to imagine, as they are really only of historic interest to-day.

The detailed description of the many and varied abdominal operations is a great feature of this book and one that will appeal to all young surgeons who are studying for higher degrees.

There can be little doubt that this important work will still be as popular as the former editions.

Keratoplasty. By R. TOWNLEY PATON, M.D., F.A.C.S., Surgeon Director, Manhattan Eye, Ear, and Throat Hospital. $10 \times 7\frac{1}{2}$ in. Pp. 280 + xvi, with 87 illustrations. 1955. New York and London: McGraw-Hill Publishing Co. Ltd. 214s.

THIS beautifully illustrated monograph with 29 excellent coloured plates is devoted to the subject of corneal grafting. The various operative techniques used by the author are well portrayed and illustrated. The pre- and post-operative care of the patients undergoing keratoplasty are discussed in a very practical manner.

Dr. Paton evidently prefers definite procedures for lamellar and penetrating keratoplasty, but he gives a very fair description of alternative methods. His results in a series of 365 corneal grafts are truly excellent.

The work of the eye-bank for sight restoration in collecting and distributing donor tissue used for corneal grafting is discussed in detail and makes fascinating reading.

The history of keratoplasty is given and an extensive bibliography completes the volume.

An outstanding book full of excellent black-and-white photographs which could not be bettered.

The Back and Its Disk Syndromes. Including Injuries, Diseases, Deformities, and Disabilities. With Notes on The Pelvis and Coccyx. By PHILIP LEWIN, M.D., F.A.C.S., F.I.C.S., Professor Emeritus and Formerly Chairman of Orthopædic Surgery, Northwestern University Medical School. Second Edition. $9\frac{1}{4} \times 6$ in. Pp. 942, with 371 illustrations and 4 coloured plates. 1955. London: Henry Kimpton. £6 15s.

THE second edition of this comprehensive volume has been completely revised and in parts rewritten and much new material has been added. Every aspect of backache has been covered, and the various and many syndromes have been thoroughly investigated. Although the diagnosis and treatment of disk lesions take up a large part of this book, yet the other injuries, diseases, deformities, and disabilities of the spine all receive adequate attention.

An excellent reference volume.

A Handbook of Modern Operative Surgery. With Chapters on Instruments, Splints, and Bandaging. By K. DAS, M.B. (Cal.), F.R.C.S. (Eng. & Edin.), Associate Professor of Surgery and Surgeon, R. G. Kar (Carmichael) Medical College Hospitals; etc. Second edition. $9\frac{3}{4} \times 6\frac{1}{4}$ in. Pp. 320 + viii, with 246 illustrations and 14 plates. 1955. Calcutta: Hilton & Co. 40s.

IT is over five years since this book appeared and the recently published second edition is not only well revised but includes new chapters on anæsthesia, operation-room technique, pre- and post-operative care, and on such procedures as skin-grafting and splinting. There are many new illustrations. In the next edition still further revision might be undertaken; instead of the advice to tie the vein accompanying a large artery, the advantages of division of the artery between ligatures over ligation in continuity might be stressed. In a small book such as this, pictures of Syme's abscess knife,

Cawardine's and Lane's clamps, some of the old splints, a section on periarterial sympathectomy, and certain other outdated procedures might be omitted. Although there are a few obvious criticisms such as these, there is much in this book to help the student and young intern, and Professor Das is to be congratulated on presenting his students with this very practical and workaday handbook.

Proctologic Anatomy. By R. V. GORSCH, A.B., M.D., F.I.C.S., F.A.P.S., D.A.B.P., Clinical Professor of Proctology, New York Polyclinic Medical School and Hospital. Second edition. 9 × 6 in. Pp. 310 + xvi, with 155 illustrations. Baltimore: Williams & Wilkins Co. (London: Baillière, Tindall & Cox Ltd.) 61s. 6d.

THE second edition of Dr. R. V. Gorsch's well-known text-book has appeared after an interval of nearly fifteen years and will be sincerely welcomed, particularly since the first edition has for a long while been out of print and unobtainable. In the preface the author insists on the importance of a detailed and accurate knowledge of anorectal anatomy as the basis for good surgery in this region, and with this all will agree. Every aspect is carefully considered in this book, with a wealth of detail and clear illustrations.

The author has taken special care in describing the anatomy of the anal canal and its musculature. We note that he teaches that the dentate line marks the upper limit of the anal canal; although this is doubtless correct from the embryological aspect, most surgeons find it an advantage, especially in the surgery of fistulæ, to consider that the anal canal extends up to the level of the anorectal ring. It is perhaps a pity, too, that the work of Eisenhammer and more recently of Goligher and others on the internal sphincter could not have been incorporated; it is now generally accepted that the tight fibrous lower border of the internal sphincter constitutes the muscle bar which has to be divided in the cure of chronic anal fissures, and that this is identical with the pecten band of Miles—that mysterious and oft-debated structure.

The old anatomical description of Milligan and Morgan relating to the muscles exposed in the course of hæmorrhoidectomy is retained without comment, although, as readers of this JOURNAL are now aware from recent papers, some modifications have been found necessary. Under anæsthesia the subcutaneous external sphincter has been proved to relax outside the field of a ligature operation and has not the importance originally assigned to it. The longitudinal muscle and its terminations are still of great importance surgically from several aspects and so is the internal sphincter. This is, in fact, an excellent subject for discussion and argument!

The post-anal spaces, superficial and deep, are described and the work of Courtney is acknowledged. The difficult subjects of the pelvic fascia and the perineopelvic spaces are described in great detail, and here we find familiar names such as Colles, Denonvillier, and Waldeyer. The lymphatic and nerve supplies of the rectum are described together with their surgical applications. The importance of the anal intramuscular glands is duly noted and the tendency of infections in them to lead to 'closed' abscesses extending into the perianal or perirectal spaces.

Dr. Gorsch has produced a learned, interesting, and beautifully illustrated work which will, we feel sure, be studied and discussed by all surgeons who have to do or teach rectal surgery. The references, too, will prove to be of great value, especially to the younger men and to anyone who wishes to do a research on any particular aspect of anorectal anatomy, and it is nice to see the old classical writings referred to so precisely as well as more recent papers.

Arthroplasty. By ST. J. D. BUXTON, M.B., B.S., F.R.C.S., Consulting Orthopædic Surgeon to King's College Hospital, etc. 8½ × 5½ in. Pp. 126 + viii, with 43 illustrations. 1955. London: Pitman Medical Publishing Co., Ltd. 30s.

IN this monograph, which will surely find a place in every orthopædic library, the author sets himself the double task of reviewing the progress made in arthroplasty during the last fifty years and of giving a lead for the future.

The historical section from Ollier and Murphy to the brothers Judet is full and comprehensive, and the indications, technique, and after-care of the operations which the author has found of the greatest help to his patients are well set out. His experiences with the Judet operation are described fully and the results of a series of one hundred such operations are subjected to a critical analysis. The conclusions reached will probably not find general agreement, but the methods of assessment of results, which are set out in considerable detail, will undoubtedly encourage others to follow-up their own results of similar operations with equal care.

The format is excellent and the numerous illustrations well reproduced. The full bibliography and index will prove of great value to all those who, like the author, feel that the restoration of controlled mobility to a stiff joint is one of the greatest benefits that operative surgery can bestow.

Obstetrics. By J. P. GREENHILL, M.D., Senior Attending Obstetrician and Gynecologist, the Michael Reese Hospital; etc. Eleventh edition. 10 × 7 in. Pp. 1088 + viii, with 910 illustrations. 1955. Philadelphia and London: W. B. Saunders Co. 98s.

THE new eleventh edition of Greenhill's *Obstetrics* has been largely rewritten and much new matter has been incorporated. In the four years' interval since the last edition the problem of oliguria and the lower nephron syndrome has been elucidated. Fœtal erythroblastosis and the Rh factor forms an entirely new chapter in the book; also there is a special chapter on endocrine changes and diseases during pregnancy.

This large work on obstetrics gives an excellent record of modern American teaching in this branch of medicine.

Christopher's Textbook of Surgery. Edited by LOYAL DAVIS, M.D., Chairman of the Department of Surgery, Northwestern University Medical School. 10 × 7 in. Pp. 1484 + xviii, with 716 illustrations. 1956. Philadelphia and London: W. B. Saunders Co. 108s. 6d.

IT is some twenty years ago that the first edition of *Christopher's Textbook of Surgery* appeared, and from the first was considered one of the best works on surgery. Now the sixth edition has appeared under the able editorship of Loyal Davis and he has certainly upheld the high standard of the previous editions. He has gathered around him experts in every branch of surgery and they have certainly given of their best in the numerous chapters which go to make up this important work.

One of the features of this text-book is the quality and quantity of the illustrations; there are some 1359, as 716 figures, all of which have been well chosen.

We are pleased that the author considered it necessary to have a chapter devoted to "The Qualifications of a Surgeon" and that he asked Paul R. Hawley to write it. Every young surgeon on both sides of the Atlantic would do well to read this chapter and consider it carefully.

We would like to congratulate Loyal Davis and his contributors on an outstanding book.

Blood Supply and Anatomy of the Upper Abdominal Organs. With a Descriptive Atlas. By NICHOLAS A. MICHELS, M.A., D.Sc., Professor of Anatomy, Jefferson Medical College, Philadelphia. 10 × 7 in. Pp. 581 + xiv, with 172 illustrations, including 166 in colour. 1955. London: Pitman Medical Publishing Co. Ltd. £8.

THIS large volume contains an extensive survey of the literature dealing with the blood-supply and anatomy of the upper abdominal organs, and with this there is a comprehensive descriptive atlas comprising 172 illustrations, of which 166 are in colour.

Every conceivable abnormality in the blood-supply of the upper abdominal organs is described and variations which are all too common in the branches of the cœliac axis artery.

Professor Michels has spent six years in dissecting 200 bodies in order to obtain an accurate account of the various vascular abnormalities.

The real value of this work will be as a reference volume to which the anatomist and the surgeon may turn to elucidate variations of the vascular pattern in the upper abdomen.

It is a pity in a large work such as this that some of the references are inaccurate.

Analgesia for Midwives. By HILDA ROBERTS, M.R.C.S., F.F.A. R.C.S., D.A., D.C.H., Hon. Research Assistant, Institute of Obstetrics and Gynæcology, Hammersmith Hospital, London. 8½ × 5½ in. Pp. 68 + viii, with 25 illustrations and 5 coloured plates. 1955. Edinburgh: E. & S. Livingstone Ltd. 10s. 6d.

DURING the last decade, the midwife's armamentarium for the alleviation of pain and discomfort in childbirth has been greatly strengthened by the addition of pethidine and trilene inhalation analgesia. Dr. Roberts deals with all aspects of the treatment allowed by the Central Midwives Board, and the excellent script is illustrated by a series of good diagrams and photographs.

This short manual is well produced and may be confidently recommended to all practising midwives and also candidates for the C.M.B. examination.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

Cardiovascular Innervation. By G. A. G. MITCHELL, O.B.E., T.D., M.B., Ch.M., D.Sc., Professor of Anatomy and Director of the Anatomical Laboratories in the University of Manchester. With a Foreword by Sir GEOFFREY JEFFERSON. 9¾ × 6¾ in. Pp. 356 + xii, with 217 illustrations, many in colour. 1956. Edinburgh: E. & S. Livingstone Ltd. 55s.

Outline of Orthopædics. By JOHN CRAWFORD ADAMS, M.D. (Lond.), F.R.C.S. (Eng.), Consultant Orthopædic Surgeon, St. Mary's Hospital, London, etc. 8½ × 5½ in. Pp. 423 + viii, with 299 illustrations. 1956. Edinburgh: E. & S. Livingstone Ltd. 32s. 6d.

Alfred Hospital: Clinical Reports, 1955. Edited by R. S. LAWSON. 9¾ × 6 in. Pp. 125 + vi. Illustrated. 1955. Melbourne: The Alfred Hospital.

Diseases of the Nose, Throat, and Ear. A Handbook for Students and Practitioners. By I. SIMSON HALL, M.B., Ch.B., F.R.C.P.E., F.R.C.S.E., Surgeon to the Royal Infirmary, Edinburgh. Sixth edition. 7¼ × 4¾ in. Pp. 463 + xii, with 84 illustrations and 6 coloured plates. 1956. Edinburgh: E. & S. Livingstone Ltd. 20s.

Clinical Neurosurgery. Proceedings of the Congress of Neurological Surgeons, New York, N.Y., 1954. 9 × 6 in. Pp. 173 + x, with 54 illustrations. 1955. London: Baillière, Tindall & Cox. 54s.

Le Cancer du Plancher de la Bouche. By MARCEL DARGENT and JEAN PAPILLON, with the collaboration of J.-F. MONTBARBON. With a Foreword by P. SANTY. 9⅞ × 6⅜ in. Pp. 169 + vi, with 48 illustrations. 1955. Paris: Masson & Co. 1,800 fr.

Chirurgie des Glandes Salivaires. By HENRI REDON, Paris. 9½ × 6¾ in. Pp. 281 + iv, with 77 illustrations. 1955. Paris: Masson & Co. Paper, 2,300 fr.; Cloth, 2,900 fr.

Management of Pain in Cancer. Edited by M. J. SCHIFFRIN, Ph.D., Chicago. With a Foreword by WARREN H. COLE, M.D. 6⅞ × 4¾ in. Pp. 245, with 10 illustrations. 1956. Chicago: Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 33s.

Advances in Pediatrics. Vol. III. Edited by S. Z. LEVINS, Cornell University Medical College, New York. 8⅛ × 5¾ in. Pp. 273. Illustrated. 1956. Chicago: Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 62s.